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Gait Initiation in Parkinson's Disease: The Interplay of Dopamine and Postural Control

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Chapter 1

Introduction

1.1 Parkinson's Disease

Parkinson's Disease (PD) is a neurodegenerative disease manifesting with motor and non-motor symptoms in a progressive course over years. "An essay on the shaking palsy" by the British physician James Parkinson published in 1817 is considered to be its first description in western literature. His definition of what he called "paralysis agitans" reads as follows:

> Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured [108].

Definition, pathophysiological comprehension, clinical semiology and available treatments of PD have undergone fundamental changes since 1817. Insights into its pathophysiology have fundamentally shaped our comprehension of extrapyramidal motor control. However, a multitude of unanswered questions remain, provoking further research trying to deepen our insight into this disease.

1.1.1 Epidemiology

PD is the second most common neurodegenerative disease. The prevalence in Europe has been estimated between 108 to 257/100,000, while its incidence has been approximated between 11 to 19 cases/100,000/year [19]. As PD commonly affects patients in later years of life and rarely occurs in subjects younger than 40 years

old, the prevalence in subjects older than 60 years is significantly higher than the general population and has been estimated between 1280 to 1500/100,000 [19, 126]. Therefore it can be expected that more than 1% of the elderly population suffer from PD. Furthermore, it has become evident, that prevalence and incidence of PD in North America have been on the rise in recent years, thus further emphasizing the relevance of PD for the aging western societies [87].

1.1.2 Clinical Presentation

The clinical hallmark of PD is its motor manifestation: bradykinesia in combination with a rest tremor or rigidity or both, which has first been described in its archetypical form by Jean-Martin Charcot in 1872 [45].

The current clinical criteria for the diagnosis of PD as proposed by the Motor Disorder Society (MDS) describe each symptom as follows: bradykinesia is defined as a "slowness of movement and progressive decline in amplitude or speed as movements are continued". The typical rest tremor in PD occurs in a frequency between 4 to 6 Hertz and it is suppressed during initiation of a movement. Rigidity in PD is a velocity-independent resistance to passive movement commonly described as "lead-pipe" resistance and has to be distinguished from other phenomena manifesting with increased muscle tone e.g. spasticity. [70, 112]

Traditionally postural instability was considered to be another core feature of parkinsonism, but has been excluded from the diagnostic criteria for PD as it usually occurs in later stages of the disease [43, 60, 112]. Nevertheless, the manifold disturbances of gait and posture associated with the disease remain a major concern. These include among others Freezing of Gait (FoG), an "episodic inability to generate effective stepping", camptocormia, an "abnormal flexion of the trunk, that appears when standing or walking and disappears in the supine position" and recurrent non-syncopal falls, occuring even in early stages of the disease [8, 44, 73]. Further motor symptoms in PD can manifest in bulbar dysfunction, i.e. dysarthria and dysphagia, reemergence of primitive reflexes, most prominently the glabellar reflex, and diverse neuro-opthalmological abnormalities [16, 69].

In recent years an increasing amount of research was conducted into the wide range of non-motor manifestations of the disease [21]. These manifestations include neuropsychiatric symptoms such as cognitive impairment, depression, delirium and sleep disorders, autonomic symptoms such as orthostatic hypotension, urogenital disturbances and xerostomia, gastrointestinal symptoms as constipation, sensory distur-

bances as anosmia or less specific symptom complexes like fatigue [22]. Occurrence of these symptoms varies across patients and the course of the disease and can eventually precede the first motor manifestations for several years. Recently, the term "prodromal" PD has been coined and defined to describe these early stages of PD yet lacking motor symptoms [7, 111].

Once a diagnosis is established the disease usually progresses over time with continuously increasing severity of symptoms and patients' discomfort. Hoehn and Yahr proposed a clinical staging system that is still in use today and correlates well with the progression of neurodegeneration [55, 15].

1.1.3 Pathophysiology

The pathophysiological hallmark of PD are Lewy Bodies, eosinophilic intracytoplasmatic proteinaceous inclusions, as well as dystrophic neurits, that contain accumulated α-synuclein [40, 121]. PD is therefore considered a *synucleinopathy* similar to multi system atrophy and dementia with Lewy Bodies. It remains unclear whether Lewy Bodies are the culprit or a result of the pathologic processes involved [35]. In PD neurodegeneration progresses in a characteristic stage-dependent pattern. In very early stages cell loss is evident primarily in structures in the lower brain stem, e.g. the motor nucleus of the vagus nerve. Once motor symptoms appear, it has usually advanced across the midbrain nuclei, in particular the pars compacta of the substantia nigra supplying the striatum with dopaminergic afferents. In late stages Lewy Bodies are also present in neocortical areas [15]. Recent evidence suggests that neurodegeneration in PD exceeds the central nervous system, as deposits of α-synuclein could be identified in peripheral nerve fibers [31]. This supports the emerging paradigm identifying PD as a multi-systemic disorder of the nervous system.

Idiopathic PD is a sporadic disorder and the mechanism responsible for the accumulation of α-synuclein and subsequent neurodegeneration remains poorly understood. Although pathogenic genes such as PARK 1-11 and LRRK2 cause an hereditary disease with a phenotype similar to idiopathic PD, these diseases are considered to be a distinct entity [98, 133]. Mitochondrial dysfunction, oxidative stress as well as impairment of the ubiquitin-proteasome-system have been suggested as possible mechanisms contributing to the molecular pathophysiology of PD [98].

1.1.4 Diagnosis

The diagnosis of PD is considered to be a clinical diagnosis, as definitive diagnosis can only be established by histopathological evaluation after the demise of the patient. Numerous other disorders of the nervous system such as other neurodegenerative disorders (e.g. progressive supranuclear palsy or multi system atrophy), structural lesions secondary to ischemia or inflammation as well as exposure to certain drugs can elicit akinetic-rigid symptoms, which calls for a careful review of the differential diagnosis [43, 60, 112, 124]. Of note, up to 15% of the patients initially diagnosed with PD do not suffer from the disease and up to 20% of PD patients are not diagnosed even after receiving medical attention [119].

In early and mid-stage PD a dramatic improvement of motor symptoms after treatment with levodopa is expected and considered a diagnostic cornerstone. This is commonly objectified in a so-called "levodopa challenge" test. In this diagnostic evaluation the motor impairment is quantified via part III of the Unified Parkinson's Disease Rating Scale (UPDRS) by an experienced clinician before and after intake of an appropriate dosage of levodopa and expected to improve by at least 30% in patients with PD [24, 47]. Other effects related to dopaminergic medication which are characteristic of PD are wearing-off-phenomena and levodopa-induced dyskinesias. Their occurence as well as their absence can be taken into consideration for the differential diagnosis [112].

A broad range of ancillary diagnostic tests for PD have been proposed and are used more or less frequently in clinical practice [124]. Nevertheless, only olfactory testing and metaiodobenzylguanidine scintigraphy investigating autonomous cardiac innervation have met the specificity thresholds to be included in the current MDS criteria [112]. Most experts in Germany still recommend routine structural brain imaging to exclude certain secondary forms of parkinsonism [102]. Molecular imaging techniques assessing the presynaptic innervation of the striatum can also aid the diagnostic process. This will be discussed separately in section 1.2.

1.1.5 Therapies

All currently established treatments of PD are targeted on symptomatic benefit as the need for a causal neuroprotective treatment remains unmet [75]. The first reliable pharmacologic treatment has been levodopa, a monoamine precursor for dopamine. Since its first application in PD patients in 1961 the benefit of several additional drugs such as dopamine agonists, Monoamine Oxidase B (MAO-B) in-

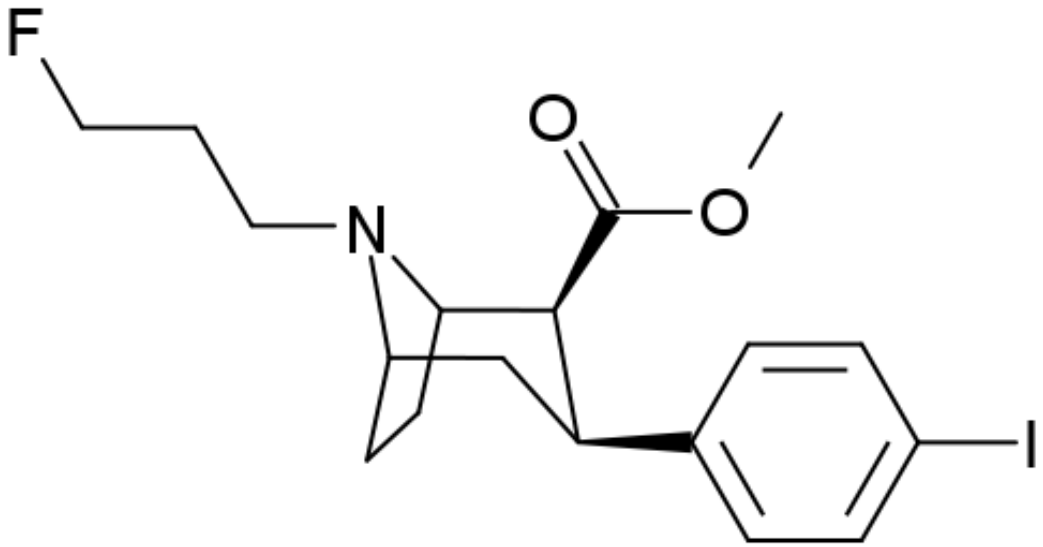


Figure 1.1: Chemical structure of FP-CIT.

hibitors and Catechol-O-Methyltransferase (COMT) inhibitors has been established [59, 78]. These drugs are used in addition to levodopa substitution therapy mostly depending on the individual patient's needs. As the disease progresses and motor complications occur advanced therapies such as Deep Brain Stimulation (DBS) or infusional therapies can be considered. In any case, physiotherapy and other supportive paramedical therapies are considered valuable and generally recommended [42, 46, 76].

1.2 Molecular Imaging in Parkinson's Disease

Positron Emission Tomography (PET) and Single-photon Emission Computed Tomography (SPECT) are non-invasive techniques for molecular imaging studies in vivo. Both techniques use tracers, that have been radioactively labeled with radionuclides. Gamma radiation, which is either directly emitted by the tracer (SPECT) or induced by positron emission of the tracer (PET), is detected by specialized cameras and allows for quantification of the specific binding potential of the tracer in a brain region of interest [62, 74, 109].

In the past decades a multitude of molecular imaging tracers have been investigated in relation to PD. Most of these tracers target the dopaminergic system, while imaging of other neurotransmitter systems has also shown relevant alterations in subjects with PD [82, 94, 107, 110]. Metabolic imaging with [^{18}F]-Fludeoxyglucose-PET also

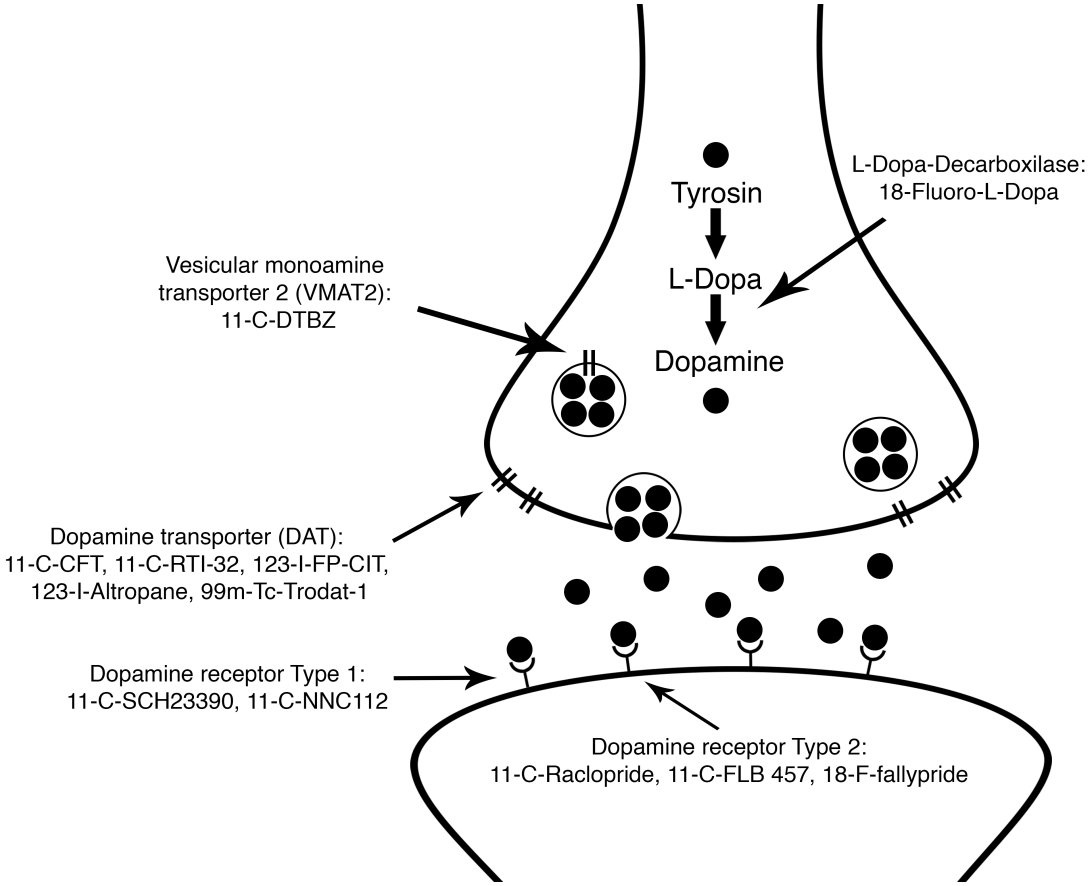


Figure 1.2: A schematic illustration of the dopaminergic synapsis depicting the target structures of commonly used molecular tracers. [82]

revealed a disease-specific pattern, which has proven useful in differentiation of PD and atypical parkinsonian syndromes [33, 34].

The most commonly used tracers targeting structures of the dopaminergic synapsis are illustrated in figure 1.2 [82]. The tracer, which is best established in Europe, is the cocaine analogue [^{123}I]-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (FP-CIT), that is also known as Ioflupane I 123 and marketed as DaTSCAN. It targets the presynaptic dopamine reuptake transporter (DAT), which clears dopamine from the synaptic cleft [104] (see figure 1.1). FP-CIT-SPECT can be used to assess the degree of dopaminergic denervation at the striatal end and correlates with the severity of motor symptoms [12, 113, 122]. It has been shown to be useful to differentiate PD from other tremor disorders and is commonly used to verify or exclude a neurodegenerative process in a patient with parkinsonian symptoms, especially in early stages of the disease [5, 63, 64, 104].

1.3 Gait Initiation

Gait Initiation (GI) is a complex motor task, that allows the transition from quiet stance to steady bipedal locomotion. A first scientific description of GI was presented in 1966 by Carlsöö [20]. During physiological quiet stance in healthy subjects the Centre of Mass (CoM) and Centre of Pressure (CoP) are kept closely aligned to maintain balance by an oscillating movement pattern, which can be put into analogy with an inverted pendulum [129, 130]. Uncoupling of CoM and CoP has been found to be crucial for initiation of gait by unloading of the stepping limb and generating forward momentum for the first step [49, 61, 71]. This is facilitated by Anticipatory Postural Adjustments (APA), which occur in any voluntary movement preceding postural disturbances. As these adjustments occur ahead of any postural changes and sensory feedback, a feedforward control mechanism is necessary [90]. APA follow a stereotypical spatial and temporal pattern, which is discussed in section 1.3.1 [39, 48]. The execution and impairment GI is of special interest in PD as it is specifically compromised in some patients exhibiting episodic FoG and it calls for a combination of feedforward control and sensorineural integration during movement control, that is dependent both on cognitive and motor function [28].

1.3.1 Characteristics and Terminology

For this study terminology according to the work of Ferrarin et al. was used and shall be clarifyed in this section describing the characteristics of GI as understood by the author [39].

To further describe the dynamic processes of locomotion two key concepts of biomechanical analysis need to be introduced [129]:

- **Centre of Mass (CoM):** In general physics CoM is used to describe the point in the distribution of a mass where all weighted relative positions sum up to zero. Correspondingly, if force is applied in the CoM the mass moves in direction of the force without turning. For analysis of bipedal upright gait CoM is commonly assumed to be at a fixed point in the pelvis. CoM position can thereby be approximated by referring to pelvic anatomical landmarks. [32]

- **Centre of Pressure (CoP):** CoP describes the point location of the ground reaction force, the sum of all forces exerted by the ground on a mass. For gait analysis CoP can be determined directly by dynamometric platforms detecting ground reaction force. [6]

In human bipedal gait the transition between stance and steady locomotion can be divided into distinct phases by characteristic events as listed below.

- **APA Onset:** Across past publications two main approaches can be distinguished to define APA onset . Some authors define it as the instance when the CoP trajectory abandons the initial position exceeding a predefined threshold, (e.g. [89]). Other studies have used an interactive approach based on visual inspection of the plotted CoP trajectory. Investigators identified the moment when the oscillating pattern of the CoP trajectory during quiet standing is abandoned and is superseded by a trajectory in postero-lateral direction towards the leg ultimately used to step forward (swing leg) (e.g. [67]). In this study we used the second, interactive approach, as subjects with PD can display altered patterns of GI leaving the threshold method prone to misjudgement of the correct instances and therefore unreliable.

- **Swing Heel Off:** The instance when the heel of the swing leg is lifted. The postural adjustments involved prompt a change of direction of the CoP trajectory, which proceeds mainly in a medio-lateral direction towards the leg providing support during the first step (stance leg).

- **Swing Toe Off:** The instance when the swing leg looses ground contact leaving the stance leg as sole weight support.

These events can be used to distinguish distinct phases of GI.Three phases of GI are described referring to the CoP and CoM trajectories [39, 66] :

- **Imbalance:** The CoP is displaced backwards and towards the swing leg generating forward acceleration of the CoM eventually generating momentum for the resulting first step.

- **Unloading:** The CoP trajectory is directed towards the stance leg unloading the swing leg for imminent lift-off.

- **First Step:** Locomotion is initiated by accelerated anterograde propulsion of the CoM with concomitant transition of CoP.

The utilized terminology for GI is illustrated in figure 1.3.

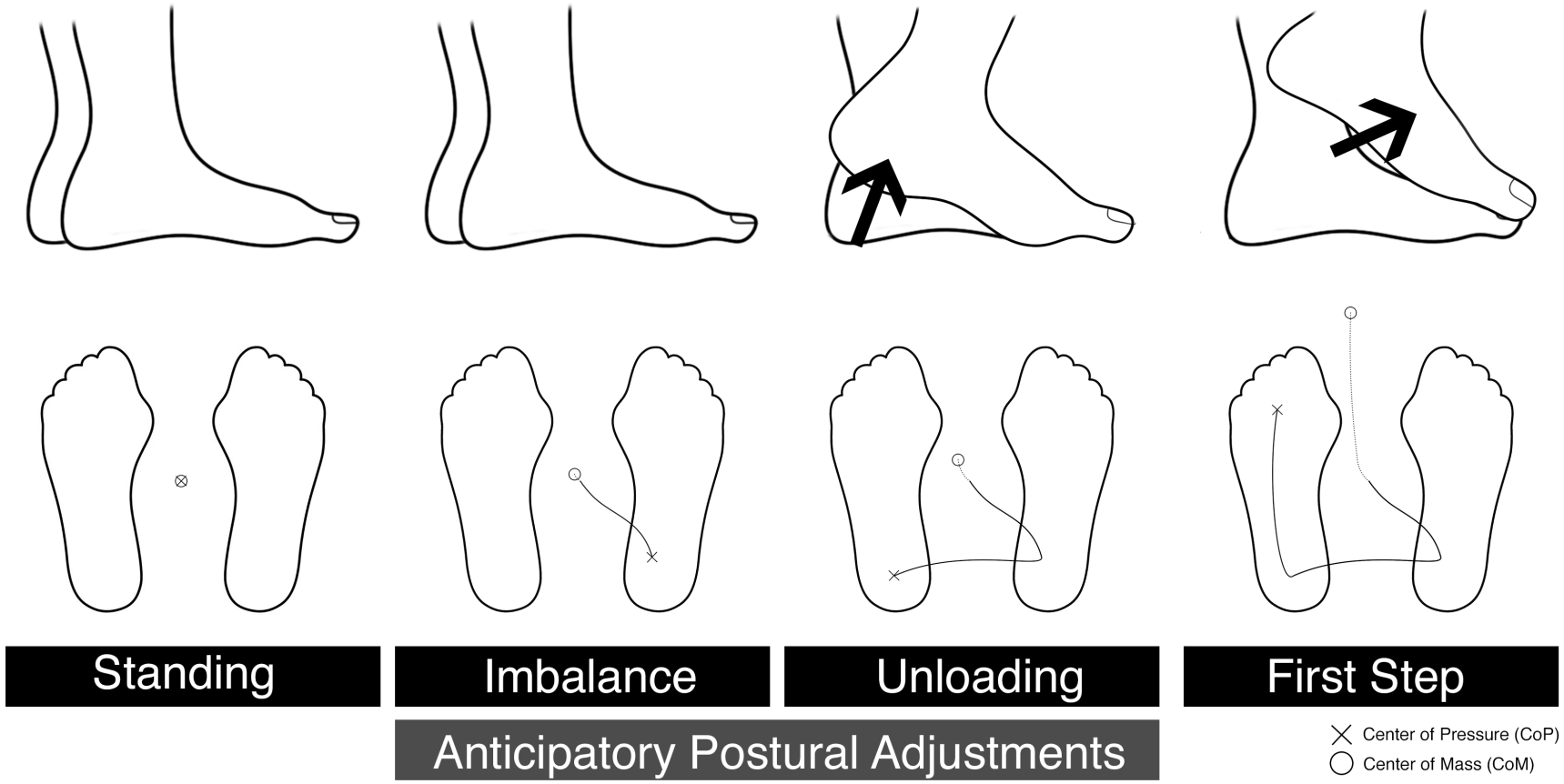


Figure 1.3: Phases of Gait Initiation. Upper Row: Feet positions indicating Heel Off (HO) and Swing Toe Off (STO). Lower Row: Diagram of typical trajectories of CoP and CoM during GI.

1.3.2 Anticipatory Postural Adjustments

APA precede any volitional movement and serve to compensate for the anticipated internal disturbance of the postural equilibrium [14, 90]. These postural adjustments are described as anticipatory as they precede the postural disturbance of the movement itself and occur before or simultaneously to it. Hence, APA require a feedforward control mechanism, that is part of the motor program of the movement in question, integrating the anticipated postural disturbance with sensory feedback throughout the movement maintaining the desired postural equilibrium [90].

During APA in GI the inital posterior shift of CoP is induced by bilateral inhibition of the mm. triceps surae and subsequent acitvation of the mm. tibialis anteriores, while the lateral shift of CoP is induced by a change in hip abductor activity and stance limb knee flexion[3, 27]. While the understanding of the neural control of APA remains fragmentary the Supplementary Motor Area (SMA) has been implicated in its timing [67].

1.3.3 Gait Initiation in Parkinson's Disease

A multitude of studies have been published, that investigate GI in PD. An overview is provided in tables 1.1 to 1.3. Gait initiation and APA in PD follow the same stereotypical patterns as in healthy controls [27, 48, 18, 118]. Most authors report the amplitude of the APA to be decreased in PD [4, 18, 30, 37, 48, 80, 86, 117]. There is some dispute how the discrete directions during APA are affected in PD. Some studies show decreased anteroposterior APA [11, 29, 50, 105], others showed decreased amplitudes for mediolateral APA [10, 67, 85, 115]. Fernandez et al. published results demonstrating a significant decrease in APA amplitude for both directions in PD [37]. Rocchi et al. could show the amplitude of APA in mediolateral direction to be inversely correlated with severity of motor symptoms. Publications discerning imbalance and unloading phase showed decreased APA amplitudes in both directions for imbalance, while during unloading only ML amplitude was reduced [37, 101].

While many authors demonstrated increased durations of APA, some recent studies failed to detect a change of APA durations in PD [4, 10, 86, 123]. All studies listed in tables 1.1 to 1.3 using optoelectronics described decreased length, velocity and acceleration for the first step in PD. Variability of the first step has been reported to be increased in PD [116].

Year	First Author	Journal	Method	Controls	FOG	Condition	n(PD)	Disease Duration	UPDRS III	Hoehn Yahr	Intervention
2018	Lu [83]	Neurology	Force Plates		+	OFF	10	7.7 + 4	39.2 + 17.2	II-III	TCS (SMA)
2017	Lu [83]	Arch Phys Med Rehabl	Force Plates		+/-	OFF	11/14	7.8 + 3.4/4.7 + 3.4	30.7 + 8.0/ 29 + 11.5	n/a	Multiple cues
2017	Ly [84]	Conf Proc IEEE Eng Med Biol Soc.	EEG		+	OFF	5	n/a	n/a	n/a	n/a
2017	Fernandes [36]	Motor Control	EMG			n/a	n/a	n/a	n/a	n/a	Dual task
2017	De Lima-Pardini [79]	Sci Rep	Feet forces/ fMRI	+		n/a	8	5.6 + 2.2	32.3+7.6	n/a	Passive supine leg raise
2017	Bonora [11]	Gait Posture	Force plates/ Optoelectronics/ IMU	+		OFF	10	n/a	27.5+9	II-III	Auditory cue
2016	Beaulne-Séguin [4]	Gait Posture	Force plates	+	+/-	ON	12/13	7.9+5.3/5.4+3.8	n/a	n/a	Conflicting cues
2016	McVey [93]	Int J Neurosci	Video	+		n/a	10	n/a	n/a	n/a	Posterior waist pull
2016	McCandless [92]	Gait Posture	Force plates/ Optoelectronics		+	OFF	20	11.5 (11-23)	n/a	n/a	Cueing devices
2016	Mancini [86]	Gait Posture	Force plates/ Optoelectronics/ IMU	+		OFF	10	8.5+3	27.5+9	II-III	n/a
2016	Lin [80]	J Neurol Phys Ther	Force plates/ Optoelectronics	+	+	ON	15	8.1+6.1	n/a	II-III	n/a
2015	Cohen [25]	Neurorehabil Neural Repair	Force plate			ON	20	6.6+4.2	26.1+7.4	II-III	Postural instructions
2015	Chong [23]	Acta Neurol Scand	Interview		+/-	n/a	n/a	n/a	n/a	II-IV	n/a
2015	Bonora [10]	J Neuroeng Rehabil.	Force plates/ Optoelectronics/ IMU	+		ON	11	8.1+3.6	17.6+5.9	II-III	Stepping upwards
2014	Delval [29]	Clinical Neurophys	Force plates	+	+/-	OFF/ON	30/30	16(12-23)/ 1(1-3)	25(16-33), 21(18-25)	n/a	Auditory cue

Table 1.1: Relevant publications on GI in PD - Table 1.

Year	First Author	Journal	Method	Controls	FOG	Condition	n(PD)	Disease Duration	UPDRS III	Hoehn Yahr	Intervention
2014	Mazzone [91]	Gait Posture	Force plates/ Optoelectronics	+		ON	n/a	n/a	n/a	n/a	PPN DBS
2014	Tard [123]	Parkinsonism Relat Disord	Force plates	+	+/-	ON	15/15	11.5+3.9/ 4.0+3.8	20.7+9.4/16.4+9.0	n/a	Auditory and visual cue
2013	Amano [1]	Parkinsonism Relat Disord	Force plates/ Optoelectronics			ON	45	7.9+5.5	22.8+5.9	II-III	n/a
2013	Fernandez [37]	Gait Posture	Force plates/ Optoelectronics	+		ON	31	n/a	25+7	n/a	n/a
2013	Vallabhajosula [125]	Gait Posture	Force plates/ Optoelectronics	+		n/a	11	n/a	n/a	n/a	Rotation
2013	Creath [26]	J Neuroeng Rehabil	Force plates	+		ON	15	8.1+2.5	n/a	II-III	Self-triggered assistive stimulus
2013	Nocera [103]	J Rehabil Res Dev	Force plates	+		ON	13	n/a	21.0+2.7	I-II	Dual task
2012	Rocchi [114]	J Neurosurg	Force plates/ Optoelectronics	+		OFF/ON	38	12.2+7.2	48.9+15.6	II-III	DBS
2012	Fernandez-del-Olmo [38]	Mov Dis	EMG	+		ON	13	4.3	16.8+8.6	I-III	Auditory and visual cue
2012	Bultitude [17]	Front Neurol	Reaction time	+		ON	16	6.1+1.3	15.7+2	n/a	Prism
2012	Roemmich [116]	Gait Posture	Optoelectronics	+		ON	46	6.9+0.8	28.1	II-III	n/a
2012	Hass [51]	Gait Posture	Force plates/ Optoelectronics	+		n/a	18	n/a	n/a	n/a	Progressive resistance training
2012	Naugle [101]	Cogn Affect Behav Neurosci	Force plates/ Optoelectronics	+		ON	26	n/a	16.7+6.2	II-III	Emotional cue
2012	Muniz [100]	Gait Posture	Force plates	+		OFF/ON	6	n/a	n/a	n/a	DBS
2011	Okada [106]	Front Neurol	Force plates	+	+/-	ON	10/7	n/a	13.4+2.7/5-24	I-IV	Auditory cue
2011	Rogers [117]	Exp Brain Res	Force plates/ Optoelectronics	+		ON	8	4.3+3.2	16.8+4.5	II-III	Vertical perturbation
2011	Okada [105]	Parkinsons Dis	Force plates	+	+	ON	10	n/a	14.1+1.9	II-IV	n/a

Table 1.2: Relevant publications on GI in PD - Table 2.

Year	First Author	Journal	Method	Controls	FOG	Condition	n(PD)	Disease Duration	UPDRS III	Hoehn Yahr	Intervention
2009	Jacobs [67]	Neuroscience	Force plates	+		OFF	8	n/a	9.0-28	II-III	TCS (SMA)
2009	Mancini [85]	Eur J Neurol	Force plates/ IMU	+		OFF	11	1.5+0.1	29+1.1	I-II	n/a
2009	Mille [96]	J Neurol Phys Ther	n/a	+		n/a	n/a	n/a	n/a	n/a	Robotic lateral pull
2008	Hiraoka [52]	Electromyogr Clin Neurophysiol	Ankle flexion	+		n/a	13	n/a	n/a	n/a	Finger movement
2008	Hass [50]	Clin Biomech	Force plates	+		ON	16	n/a	21.7+1.4	I-III	n/a
2007	Mille [95]	Mov Dis	Force plates/ Optoelectronics	+		ON	8	n/a	25.1+12.77	I-III	Robotic lateral pull
2006	Rocchi [115]	Neuro Sci Let	Force plates/ Optoelectronics	+		OFF/ON	21	16.2+9.2	47+13.6	II-IV	Stance alteration
2006	Liu [81]	Gait Posture	Force plates			OFF/ON	11	n/a	n/a	n/a	STN DBS
2006	Hiraoka [54]	Parkinsonism Relat Disord	EMG	+		n/a	n/a	n/a	n/a	n/a	Auditory cue
2006	Jiang [72]	Clin Rehabil	Force plates		+/-	ON	14	4.8+3.4	n/a	n/a	Auditory and visual cue
2005	Hass [49]	Arch Phys Med Rehabil	Force plates/ Optoelectronics			ON	43	n/a	21.5+1.4	I-IV	>< HY 2,5
2005	Hiraoka [53]	Mov Dis	EMG			ON	11	n/a	23.9+4.1	II-IV	n/a
2004	Dibble [30]	Gait Posture	Force plates/ Optoelectronics	+		n/a	7	n/a	n/a	II-II	Cue
2002	Martin [88]	Phys Ther	Force plates/ Optoelectronics	+		n/a	n/a	n/a	n/a	I-III	n/a
1998	Halliday [48]	Gait Posture	Force plates/ Optoelectronics/ EMG	+	+	OFF	10	5+1	n/a	II-III	n/a
1997	Burleigh-Jacobs [18]	Mov Dis	Force plates	+		OFF/ON	6	8.0+3.4	n/a	III-IV	Cue and perturbation

Table 1.3: Relevant publications on GI in PD - Table 3.

Levodopa substitution has been shown to improve GI performance in PD with regards to APA amplitude and duration, as well as velocity and length of the first step [18, 29, 100, 115, 114]. The application of external cues in different modalities, as well as assistive postural perturbation also improve the GI performance in PD [18, 26, 29, 95, 115]. Likewise, internal cues such as finger movements or cueing devices can modulate GI in PD [52, 92] Dual tasking during GI led to less efficient step initiation in one study, while another demonstrated less efficient performance for the cognitive task in the experiment [103, 123]. The available results for the effect of DBS point to an improved GI performance during active stimulation in Globus Pallidum Internus (GPI), Nucleus subthalamicus (STN) and Pedunculo Pontine Nuclei (PPN) [81, 91, 100]. However, Rocchi et al. argued, that DBS might nevertheless be detrimental to GI in PD. While DBS had a beneficial acute effect in their population, DBS implanted subjects consistently performed worse during GI trials, than they did at baseline prior to surgery [114].

Initial standing condition have been proven to be relevant for APA and GI in Healthy Controls (HC) as well as in PD [115]. How precisely initial stance width affects GI and how stance might be affected by the disease or other confounding factors in detail remains unclear.

1.4 Goal of this Study

This study aims to refine the understanding of alterations of GI in PD in a large collective, while addressing confounding factors for GI in anthropometrics as well as initial stance. It is also designed to unravel the role of the dopaminergic system during GI in PD by comparing GI in OFF and ON condition and assessing correlations between the dopaminergic deficit in PD and the characteristics of GI. This study will establish a framework for future investigations of GI of patients with PD with specific disabilities e.g. FoG.

Chapter 2

Methods

Acquisition of biomechanical data was performed at:

- Laboratorio per l'Analisi del Movimento (LAM) at the Section of Physiology, Dipartimento di Fisiopatologia Medico Chirurgica e dei Trapianti, Universitęgli studi di Milano in Milan, Italy.
- Gait laboratory at the Neurology Department at the Universitätsklinikum Würzburg (UKW) in Würzburg, Germany.

Acquisition of molecular imaging was performed at:

- Department of Nuclear Medicine at the Ospedale Ca' Granda di Milano in Milan, Italy.
- Department of Nuclear Medicine at the Universitätsklinikum Würzburg (UKW) in Würzburg, Germany.

In both centers approval of the local ethics committee was obtained (LAM: 5/2016, UKW: AZ 36/17).

In this chapter methods and equipment of both laboratories used during data acquisition are described as well as the methods used for uniform elaboration and analysis of the data.

2.1 Subjects

Fifty-three adults participated in this study. Twenty-seven subjects with idiopathic PD and twenty-six healthy subjects with similar age and gender characteristics (HC) were investigated. The diagnosis of PD was made by an experienced movement disorder specialist according to the UK Brain Bank Clinical Diagnostic Criteria for PD [60]. Exclusion criteria included any other relevant disorder interfering with gait and balance such as major cardio- or cerebrovascular disease, dementia, vestibular disorders, diabetic or any other severe polyneuropathy as well as major orthopaedic disorders. All subjects gave written informed consent in accordance with the declaration of Helsinki.

For all subjects the following demographic and clinical information was recorded:

Demographic information

- Age
- Sex

Clinical information

- Age at onset of first motor symptoms
- Disease duration as defined by the previous item
- Hoehn and Yahr scale [55]
- UPDRS (part III) scale [47]

Of all twenty-seven patients with PD only one subject did not manage to perform the acquisitions in OFF. Thirteen of all patients (48,1 %) performed biomechanical assessment both in OFF and ON as defined below:

- OFF: Assessment after overnight suspension of all dopaminergic medication
- ON: Assessment approximately sixty minutes after intake of a water soluble preparation of 200/50 mg levodopa/benserazide.

Twenty-two patients (81,5 %) underwent a molecular imaging study within two years before or after the biomechanical evaluation as part of their clinical work up. For ten patients with PD (37 %) a complete data set was available including

biomechanical data for both medication states and imaging data. Healthy controls neither underwent nuclear imaging nor received any medication.

2.2 Biomechanical Analysis

2.2.1 Optoelectronic System

The subjects' motions during GI were captured using optoelectronic systems. Such systems allow for a precise, non-invasive measurement of movements by means of reflective markers that are recognized by a software algorithm via a designated set of cameras. Prior to assessment these small reflective markers are attached to the subjects at various landmarks according to a pre-defined protocol (see "Markerset").

Figure 2.1: Two reflective markers.

Both laboratories are equipped with the same commercially available infrared optoelectronic system (SMART, BTS, Milan, Italy). Six infrared cameras were put in place to allow for a calibration volume of 5 x 3 x 2 m. Each camera is equipped with a circular light source emitting infrared light co-axially to the camera's objective. The emitted light is then reflected by the aforementioned markers and detected by the cameras. Information about the relative positions of the cameras obtained during calibration and synchronization of camera input allow for reconstrucion of the markers' motion in space and time. Sampling rate was set at 60 Hz (LAM) or 100 HZ (UKW).

The systems of the SMART line come with a set of software designated to perform some data processing. For this study's purpose the following were used in initial data processing:

- **SMART Capture:** Software tool, which is used while recording motion data, that is stored as 2D data sequences.
- **SMART Tracker:** Software tool, that compiles the 2D data sequences from each camera and the calibration file into a 3D data set across time.
- **SMART Viewer:** Software tool, that visualizes the compiled 3D data set for inspection.

After marker identification, data compilation and inspection all post-processing was performed using the MATLAB environment as described in 2.2.3.

Calibration

An optoelectronic system records the position of each marker with respect to the sensors of each camera. To ultimately link the reference system of the cameras' sensors to the absolute common framework multiple geometric transformations are necessary. These transformations are dependent on internal and external parameters. The internal parameters are camera specific such as focal length, principal point coordinates and distortion coefficient. The external parameters depend on the positions of the cameras into relation to each other and are assessed during calibration.

During calibration a pre-specified marker arrangement is used to define a Cartesian coordinates system. In practice three wands, carrying nine markers in pre-specified positions, are placed in perpendicular position to each other and in the centre of the designated volume of calibration. At the intersection of all three trajectories, where the wands are connected to each other, the point of origin is defined. Information about the pre-specified spacings are used to obtain information about the position of each camera in relation to the point of origin. In a second step the volume of calibration is explored with a wand carrying three markers in pre-specified spacing. This allows for quality control and validation of each calibration.

Figure 2.2: One of the infrared cameras used for this study.

Markerset

To standardize motion detection in kinematic evaluation reflective markers usually are attached in a uniform manner to anatomical landmarks. The markers used for these acquisitions were spherical and 15 mm in diameter. In this study a protocol of twenty-nine markers referring to particular anatomical landmarks was used. A

Body Part	**Anatomical Landmark**
Head	Temple*
Shoulders	Acromion*
Arms	Epicondylus lateralis humeri*
	Processus styloideus ulnaris*
Chest	Processus spinosus vertebrae cervicalis VII
	Processus spinosus vertebrae thoracalis VIII
Pelvis	Centre between both spinae illiacae posteriores superiores
	Spina illiaca anterior superior*
Upper Legs	*Trochanter major**
	Thigh*
Lower Legs	*Condylus medialis tibiae**
	Condylus lateralis tibiae*
	Caput fibulae*
	Shank*
Feet	*Malleolus medialis**
	Malleolus lateralis*
	Tuber calcanei*
	*Caput ossis metatarsalis I**
	Caput ossis metatarsalis V*
	Phalanx distalis ossis digiti hallucis*

Italics indicate markers, that were removed after anatomical calibration.
* indicates bilateral landmarks.

Table 2.1: Anatomical landmarks used for the marker placement.

complete list of anatomical landmarks is provided in table 2.1 and the full set-up is shown in figure 2.3.

During anatomical calibration subjects stood still with extended arms and legs slightly rotated outwards to optimize visibility of all attached markers. This allowed for precise anthropometric measurements in all subjects. Eight markers could be removed prior to further investigations. Post-hoc reconstruction of removed markers' positions was still feasible using rigid body kinematics.

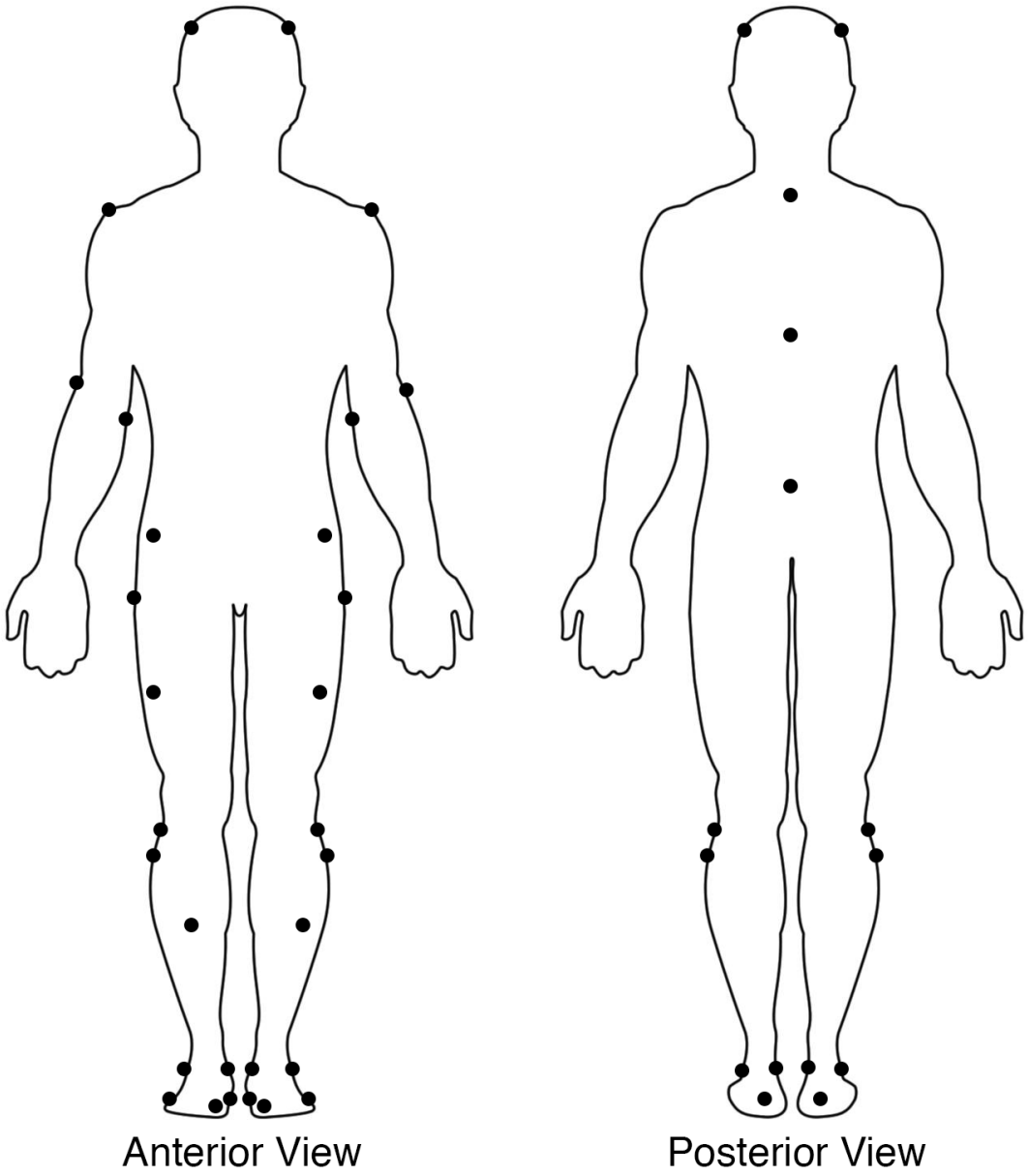


Figure 2.3: A schematic illustration of the marker model used for this study.

2.2.2 Dynamometric Platforms

Kinetic information was processed and recorded via two dynamometric platforms, also known as force plates, in ground level, that subjects stood on at the beginning of each acquisition (KISTLER 9286a (LAM)/ KISTLER 9260aa (UKW)). These force plates are equipped with piezoelectronic sensors that transform force into electric signals. These sensors are placed under each point of support - in groups of three in perpendicular orientation. Integrating the signals for all respective sensors the

force plate records the vector of the force applied to itself, respectively the ground reaction force. The point of application of this vector is understood to be the CoP.

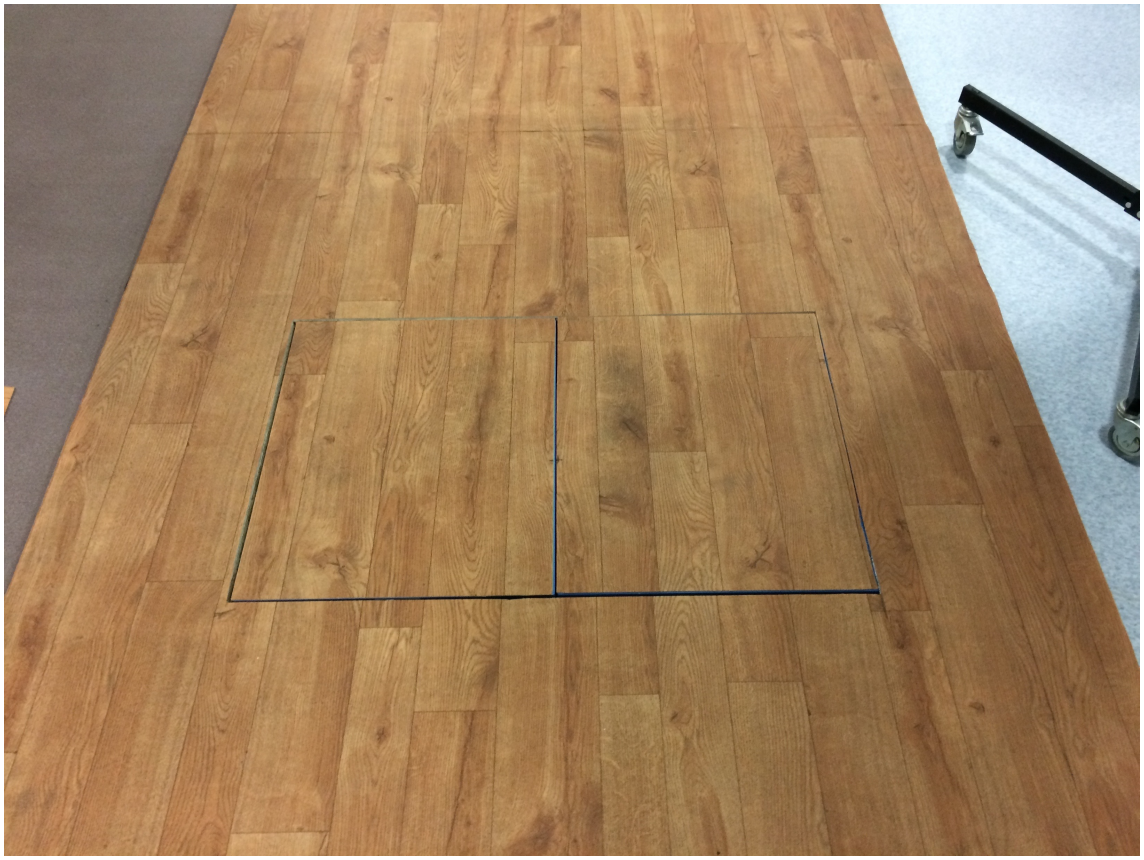


Figure 2.4: The two dynamometric platforms embedded into the walkway.

2.2.3 Experimental Set-Up

Acquisitions of gait initation were performed starting on the force plates at the centre of the volume of calibration embedded in a walkway of 11.5m (LAM) or 7.5m (UKW) length. Subjects were tested barefoot and wearing form-fitting clothes. During each acquisition the subject was instructed to stand at the centre of the force plates in a relaxed, upright manner for thirty seconds and to start walking at self selected speed after a verbal command. Feet position during standing was neither fixed nor imposed upon subjects, but it was aligned to the force plates' orientation after visual inspection by the instructor. Trials were deemed performed correctly, if the first step carried off the force plates. Specific gestures of the upper limbs e.g. crossing arms, were disencouraged.

Anthropometric Measurements

The acquisition referred to as "anatomical calibration" above was used to calculate a set of anthropometric measurements for each subject. The numerical mean of the vertical vector of the ground reaction force was transformed into each subject's body weight using an approximation of the standard gravity value. Body height was approximated adding 20% to the distance measured between the markers for processus spinosus vertebrae cervicalis VII and caput ossis metatarsalis V. Foot length was assessed determining the distance between the marker for the phalanx distalis ossis digiti hallucis and the ipsilateral tuber calcanei.The length of the lower limbs was approximated by the distance between markers for the spina iliaca anterior superior and the ipsilateral malleolus lateralis. Body mass index was calculated according to common practice using calculated body height and weight.

Kinematic and Kinetic Analysis

CoM Trajectory

Before any data elaboration, 3D marker trajectories were interpolated and filtered with a low-pass elliptic filter with a cut-off frequency of 10 Hz. After reconstruction of 3D marker trajectories the position of the CoM was interpolated using Zatsiorsky's equations published in 1982 [132]. CoM velocity was calculated via the first derivative of CoM position across time, whereas CoM acceleration was calculated via the second derivative.

CoP Trajectory

By definition the CoP trajectory can be directly extracted from force plate data using the following equation:

$$CoP_{tot} = \frac{CoP_l * R_{vl}}{(R_{vl} + R_{vr})} + \frac{CoP_r * R_{vr}}{R_{vl} + R_{vr}} \tag{2.1}$$

R_{vl} and R_{vr} are considered the vertical ground reaction forces detected by either left or right platform, whereas CoP_l and CoP_r are the CoP-vector of left and right foot, respectively [130].

The obtained pathways were filtered with an low-pass elliptic filter, with a cut-off frequency so that the 95% of the signal power spectral density (PSD) was preserved after the filtering.

Event Identification

For further analysis it was crucial to identify the characteristc events, that divide GI in its distinct phases. Most instances were identified visually by an experienced investigator after inspection of the CoP trajectory. APA onset was considered to be the instance when the trajectory of the CoP during stance first changed into a directed trajectory in posterior and lateral direction towards the swing leg, while Swing Heel Off was identified by the rapid change of direction of the trajectory towards the stance leg. The third major change of direction towards the anterograde direction was considered indicative of Swing Heel Off. All mentioned time points were used to divide GI and calculate temporospatial properties of CoP and CoM trajectories for each defined phase.

The begin of the first step was automatically identified as the instance the position of the malleolus lateralis of the swing leg moved in anterior-posterior position across a threshold defined using its position during stance, hence indicating forward motion of the swing foot. Identified events were used to subdivide GI into the aformentioned phases *imbalance, unloading* and *first step*.

Parameters

In table 2.2 all calculated parameters of GI are listed with the corresponding unit. This table also indicates the codes used for abbreviation.

Parameter	Unit	Code
Imbalance Phase		
Duration	s	IM_DUR
Absolute length of CoP trajectory	mm	IM_COP_LEN
Average velocity of CoP	mm/s	IM_COP_VEL
Mediolateral displacement of CoP	mm	IM_COP_ML_DIS
Anteroposterior displacement of CoP	mm	IM_COP_AP_DIS
Velocity of CoP (mediolateral)	mm/s	IM_COP_ML_VEL
Velocity of CoP (anteroposterior)	mm/s	IM_COP_AP_VEL
Velocity of CoM at the end of imbalance	mm/s	IM_COM_VEL
Acceleration of CoM at end of imbalance	mm/s^2	IM_COM_ACC
Distance of CoP/CoM at end of imbalance	m	IM_COM_COP_DIS
Slope of CoM/CoM vector at end of imbalance	deg	IM_COM_COP_SLO
Unloading Phase		
Duration	s	UN_DUR
Absolute length of CoP trajectory	mm	UN_COP_LEN
Average velocity of CoP	mm/s	UN_COP_VEL
Mediolateral displacement of CoP	mm	UN_COP_ML_DIS
Anteroposterior displacement of CoP	mm	UN_COP_AP_DIS
Velocity of CoP (mediolateral)	mm/s	UN_COP_ML_VEL
Velocity of CoP (anteroposterior)	mm/s	UN_COP_AP_VEL
Velocity of CoM at the end of unloading	mm/s	UN_COM_VEL
Acceleration of CoM at end of unloading	mm/s^2	UN_COM_ACC
Distance of CoM/CoP at end of unloading	m	UN_COM_COP_DIS
Slope of CoM/CoP vector at end of unloading	deg	UN_COM_COP_SLO
First Step		
Length	m	FS_SL
Average velocity of CoM	m/s	FS_VEL_AVG
Velocity of CoM at toe off of stance leg	m/s	FS_TOE_COM_VEL
Acceleration of CoM at toe off of stance leg	mm/s^2	FS_TOE_COM_ACC
Distance of CoM/CoP at toe off of stance leg	m	FS_TOE_COM_COP_DIS

Table 2.2: All parameters of GI calculated for this study.

Base of Support

We did not ask the subjects to initiate gait from a fixed position and therefore did not standardize the initial standing position or stance. It can not be excluded, that the choice of stance might be either altered by the disease itself or by a compensatory mechanism required due to its symptoms. As the physiological stance width of patients with PD can not be determined retrospectively, this was omitted intentionally to avoid any intrusion into the subjects' behavior. To account for influences of initial stance the base of support (BOS) during quiet stance was approximated. The area of the polygon outlined in figure 2.5 was calculated for each trial to be put into correlation with the other biomechanical findings.

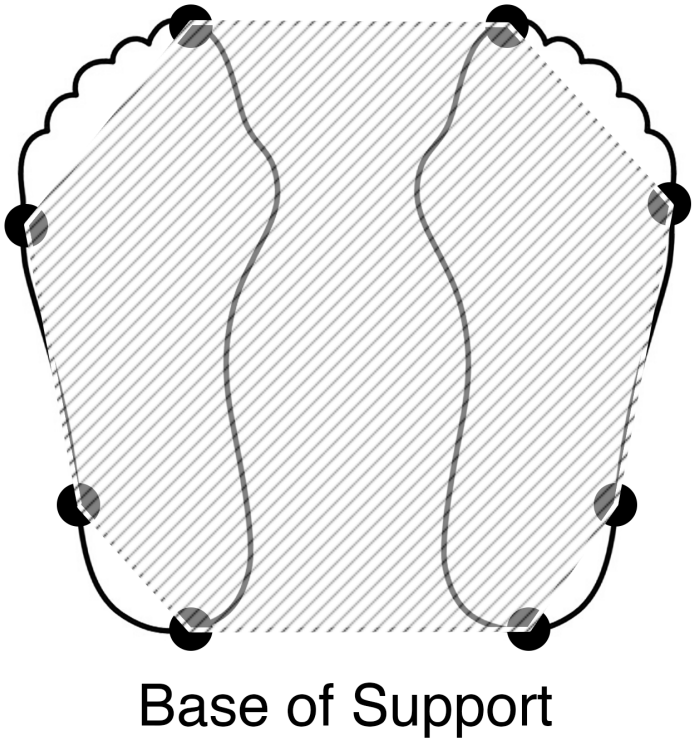


Figure 2.5: A schematic illustration of the base of support during stance.

2.3 Molecular Imaging

This study aimed specifically to identify and characterize pathological changes of GI in subjects with PD and to uncover the relationship of these changes with dopaminergic activity in the basal ganglia. Twenty-two subjects of the PD group underwent a FP-CIT-SPECT within two years of the biomechanical evaluation as part of their

clinical work up, which quantifies dopaminergic innervation of cerebral structures. Investigations followed established protocols used in clinical routine and were post processed and analyzed in an uniform manner for this study.

2.3.1 [^{123}I]-FP-CIT-SPECT

Each subject was tested under stable dopaminergic medication as Booij and Kemp concluded that there is no significant acute effect of commonly used dopaminergic medications on FP-CIT-SPECT for imaging in PD [13]. Subjects were injected with FP-CIT (DaTSCAN, GE-Health, Amersham, UK) approximately thirty to forty minutes after thyroid blocking with 630 mg sodium perchlorate administered orally. Around 180 minutes after injection SPECT was performed using a dual-headed-SPECT/CT-System (Symbia T2 SPECT Scanner, Siemens, Erlangen, Germany). Both heads were equipped with MELP (medium energy low penetration) collimators. 60 projections of 40 s each were captured with the following acqusition parameters: photopeak window of 159 keV ± 15%, matrix 128x128, zoom factor 1.23.

2.3.2 Imaging: Data Elaboration and Analysis

Threedimensonal reconstruction was performed using OSEM 3D (including resolution recovery) with 8 subsets, 8 iterations and 8 mm Gaussian filtering as suggested by Winz et al. for FP-CIT-SPECT [131]. Triple energy window scatter correction was applied. To improve data quality attenuation correction was based on low-dose CT data acquired during the same imaging session (Care dose modulation; 130 kV, slice thickness 0.5 cm, acquisition time 0.8 s; reconstructed using a B08s kernel) using the manufacturer's software (e.soft, Siemens Healthcare, Erlangen, Germany) [77].

FP-CIT binding was measured by an experienced nuclear medicine physician (Dr. J. Brumberg, Universitätsklinikum Würzburg). Visually aided segmentation and analysis was performed using PMOD, a commercially available software package (Version 3.2; PMOD Technologies Ltd, Adliswil, Switzerland). After reorientation in AC-PC direction volume of interest (VOI) delineation was performed in visual reference to three slices of each data set with maximum striatal binding. Predefined atlas based VOIs supplied by the software package were manually readjusted for size, position and rotation. Segmentation was aiming to identify caudate nucleus (CNC), putamen (PUT), the striatum (STR) as well as the SMA for each hemisphere. To assess background tracer activity due to unspecific binding of FP-CIT an additional larger reference region in the occipital lobe (REF) was defined. Specific binding

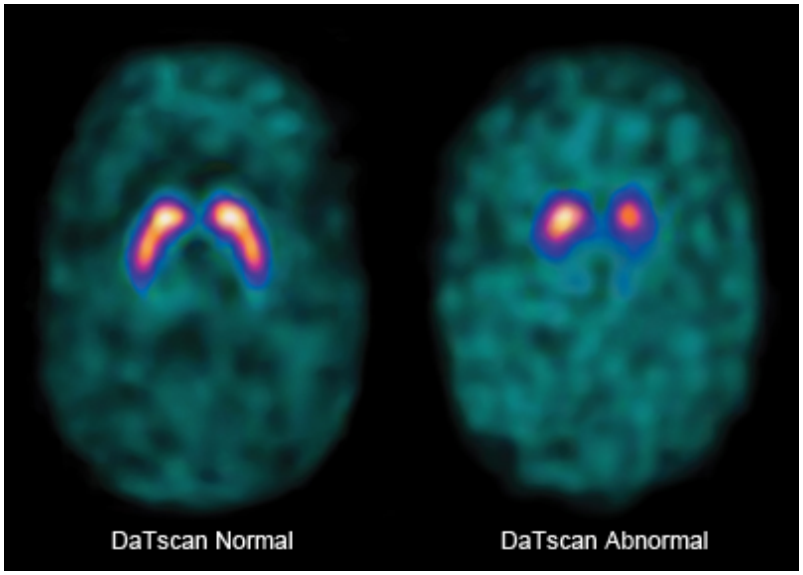


Figure 2.6: An example of a normal and a pathologically altered FP-CIT-SPECT [41].

potential (BP) for each volume of interest was then derived from averaged tracer activity (TA) in the segmented volumes using the following formula:

$$BP_{VOI} = \frac{TA_{VOI} - TA_{REF}}{TA_{REF}} \tag{2.2}$$

Cerebral structures were identified as contra- or ipsilateral in reference to the stepping leg used by the subject for each trial.

2.4 Statistical Analysis

All further statistical analysis was performed with the commercially available JMP statistical package (version 13, SAS Institute, Inc., Cary, NC, USA). For biomechanical evaluations the resulting values were averaged across at least three and up to five successful trials for each subject. All data was tested for normal distribution using the Shaprio-Wilk test and plotted in histograms for visual control. Non-normally distributed data was compared using non-parametrical statistics. Level of significance was set to 0.05.

Chapter 3

Results

3.1 Demographics and Clinical Data

Age and gender were noted and compared for HC and PD (table 3.1). Age was normally distributed for both groups and did not show a significant difference in a two-sample t-test (t(45.3)=0.02, p=0.98). Gender distribution was also comparable.

Group	n	Gender ratio (m : f)	Age (in years)
HC	26	17 : 9	61.0 ± 5.2
PD	27	19 : 8	61.1 ± 7.8

Table 3.1: Demographic data of the study population.

Mean disease duration in PD patients was 11.1 ± 5.1 years, while mean age of onset was 50.1 ± 9.1. UPDRS Part III scores could be obtained for all subjects except for subjects PD07 and PD08. Mean UPDRS score in OFF was 29.6 ± 10.0, whereas mean score in ON was 11.2 ± 5.7. All patients were moderately affected and ranking stage 2 to 3 on the Modified Hoehn Yahr Scale. A full list of the clinical properties of PD patients is provided in chapter 6 in table 6.19.

3.2 Biomechanical Analysis

3.2.1 Anthropometrics and Base of Support

Anthropometric properties were compared between groups. All parameters were normally distributed and did not differ significantly between groups (table 3.2).

Variable	**HC**	**PD**	**Z-value**	**p-value**
Body height [cm]	171.7 ± 8.3	171.1 ± 10.8	t(46.9) = -0.59	0.83
Footlength [mm]	254.1 ± 15.2	252.8 ± 16.9	t(49.5) = -1.30	0.77
Limb length [mm]	895.0 ± 43.9	889.1 ± 70.1	t(42.0) = -5.85	0.64
Body weight [kg]	75.8 ± 12.6	76.3 ± 17.0	t(46.1) = 0.54	0.90
BMI [kg/m^2]	25.7 ± 3.6	25.9 ± 4.4	t(47.9) = 0.23	0.84

Table 3.2: Anthropometric properties of study subjects.

In a multivariate analysis investigating linear correlations between the base of support and GI parameters in healthy controls on a trial-by-trial basis nine parameters could be identified, that were statistically dependent on base of support (table 3.3). These parameters were excluded from further analysis to avoid this established confounding factor.

Parameter	Rho	p-value
Imbalance Phase		
IM_COM_VEL	0.4063	**0.0394***
Unloading Phase		
UN_COP_LEN	0.5562	**0.0032***
UN_COP_VEL	0.3956	**0.0455***
UN_COP_ML_DIS	0.5966	**0.0013***
UN_COP_AP_DIS	0.4284	**0.029***
UN_COP_ML_VEL	0.414	**0.0355***
UN_COP_AP_VEL	0.6568	**0.0003***
UN_COM_VEL	0.4324	**0.0274***
First Step		
FS_TOE_COM_COP_DIS	0.5076	**0.0081***

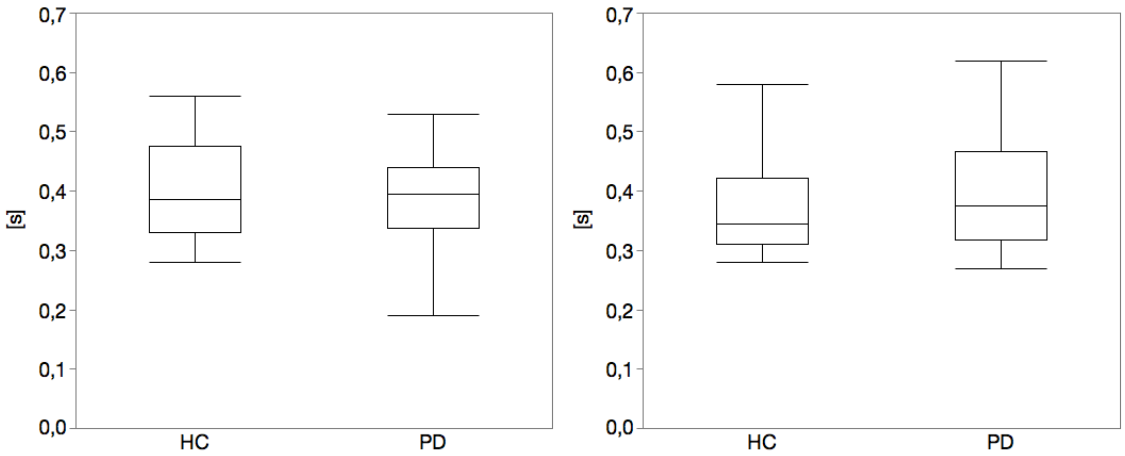
Table 3.3: Significant Spearman's Rank Order Correlations between GI parameters and base of support. Asterisk indicates significant p-value.

Correlations of all parameters with anthropometric measurements were also explored. As the length of the first step (FS_SL) correlated significantly with subject's body height an additional normalized parameter FS_SL_% (step length as percentage of the individual's bodyheight) was computed and considered during further analysis.

3.2.2 Alterations of Gait Initiation in Patients with PD

To assess and quantify changes in GI accountable to PD the remaining temporospatial parameters of GI were explored and compared for HC and PD-OFF. As normality of the available data could not be confirmed, medians and interquartile ranges are reported and the Mann-Whitney U test was used for comparison (Full results in table 3.4).

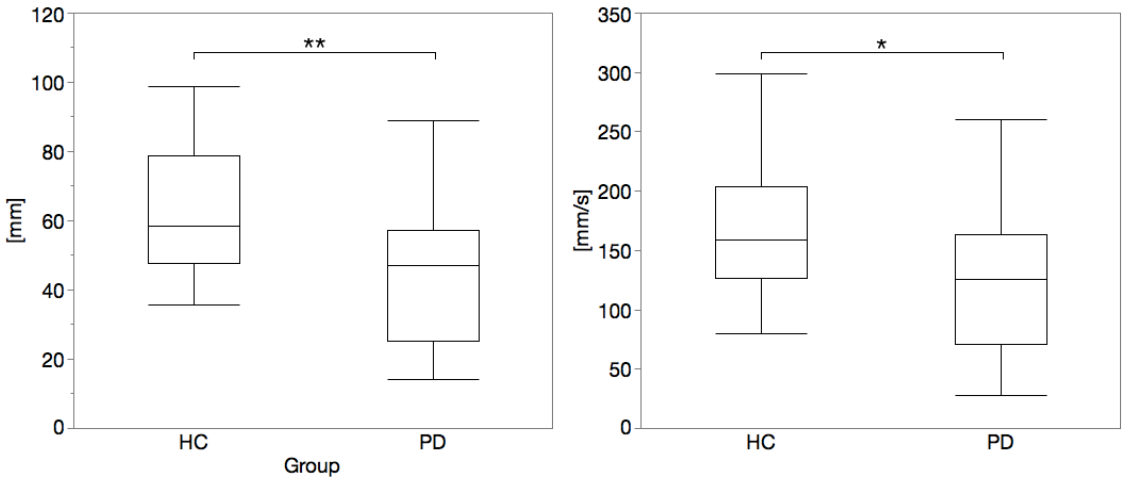
The temporal sequence of GI remained preserved in PD as duration of unloading and imbalance did not differ significantly between HC and PD. (Figure 3.1)



(a) Imbalance (b) Unloading

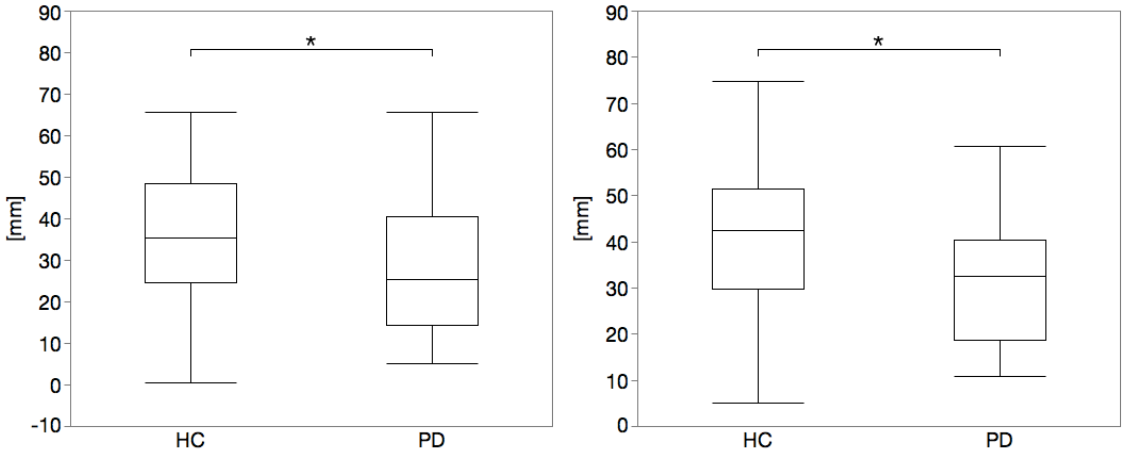
Figure 3.1: Boxplot comparison of GI phase durations in HC and PD.

During imbalance the amplitude of temporospatial parameters were significantly reduced in PD-OFF in comparison to HC (figure 3.2). Spatial extent of CoP displacement was reduced in mediolateral as well as in anteroposterior direction (figure 3.3). Significantly reduced velocities of CoP displacement were found in overall analysis and in mediolateral direction (figure 3.2b and 3.4b). Group difference for the velocity of CoP displacement in anteroposterior direction did not reach significance, but showed a clear trend ($p = 0.0659$) towards smaller values in PD (figure 3.4a).



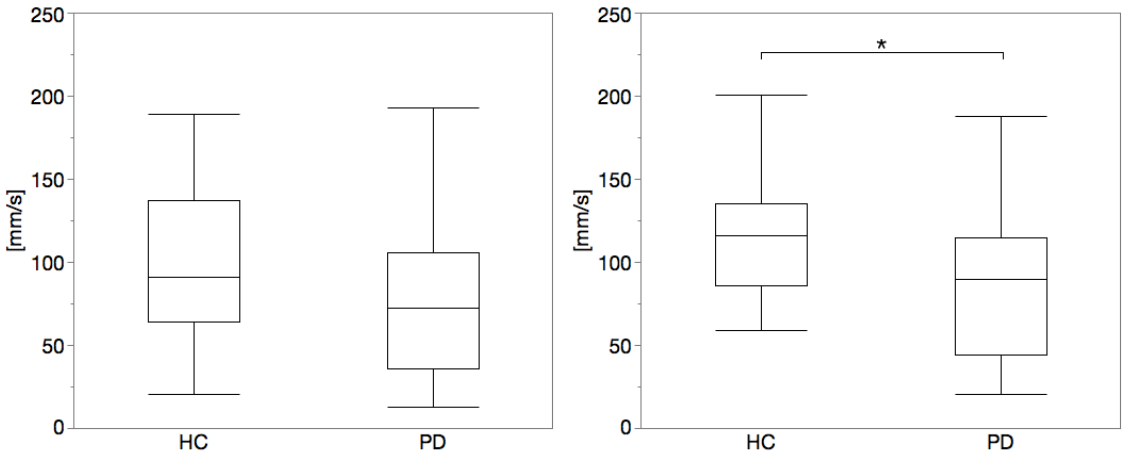
(a) Length of CoP trajectory (b) CoP velocity

Figure 3.2: Boxplot comparison of length of CoP trajectory and average CoP velocity in HC and PD during imbalance. Asterisk indicates statistically significant difference ($p < 0.05$). Double asterisk indicates statistically significant difference ($p < 0.01$).



(a) Anteroposterior CoP displacement (b) Mediolateral CoP displacement

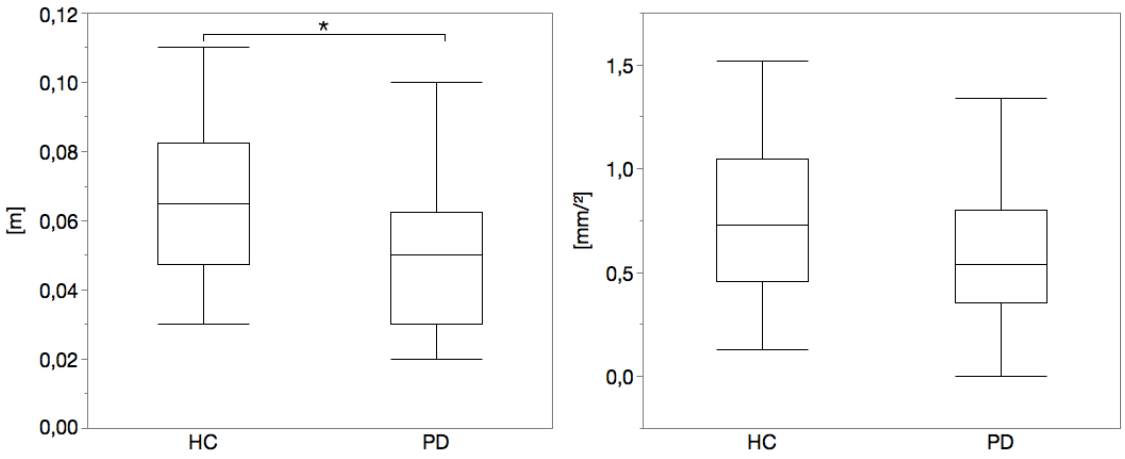
Figure 3.3: Boxplot comparison of directional CoP displacement in HC and PD during imbalance. Asterisk indicates statistically significant difference ($p < 0.05$).



(a) CoP velocity in anteroposterior direction (b) CoP velocity in mediolateral direction

Figure 3.4: Boxplot comparison of directional CoP velocity in HC and PD during imbalance. Asterisk indicates statistically significant difference ($p < 0.05$).

At the end of the Imbalance phase the distance between CoP and CoM was significantly smaller in PD-OFF. Acceleration of CoM at this time point did not differ significantly between groups, but showed a clear trend ($p = 0.0593$) towards reduced values (figure 3.7). For the slope of the CoP/CoM vector there was no group effect.

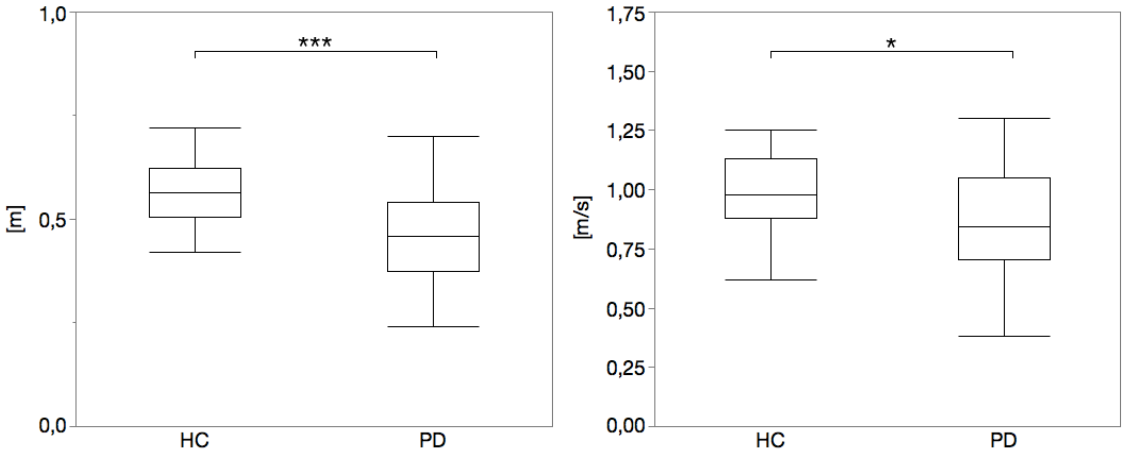


(a) Distance of CoM/CoP (b) COM acceleration

Figure 3.5: Boxplots for the specified parameters at the end of imbalance. Asterisk indicates significant group difference ($p < 0.05$).

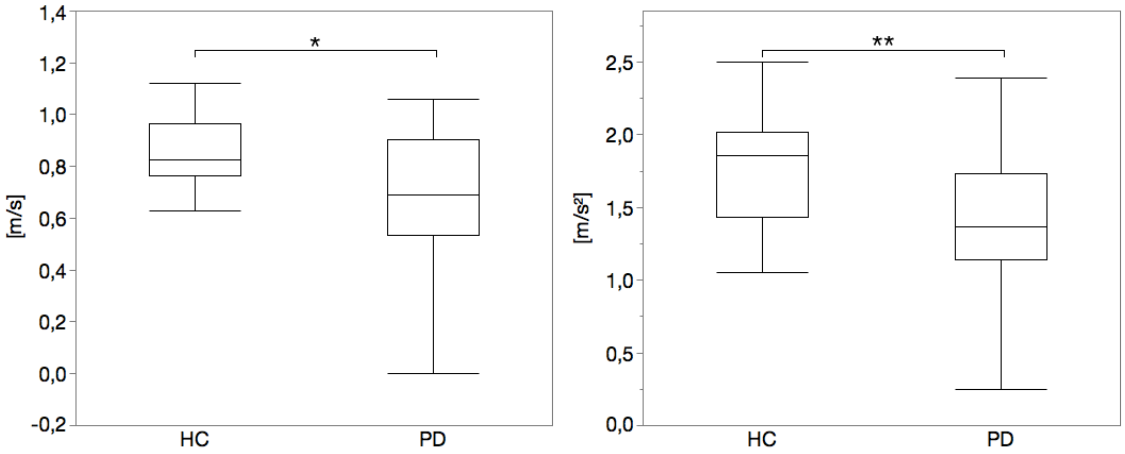
We did not find any significant difference for all parameters of the unloading phase between HC and PD-OFF.

The properties of the first step did differ significantly, as it was significantly shorter and slower in PD-OFF (figure 3.6). At the end of first step CoM velocity and acceleration were found to be significantly reduced in PD-OFF as well (figure 3.7).



(a) Step length (b) COM velocity

Figure 3.6: Boxplot comparison of step length and COM velocity during the first step in HC and PD. Asterisk indicates significant group difference ($p < 0.05$). Triple asterisk indicates significant difference ($p < 0.001$)



(a) COM velocity (b) COM acceleration

Figure 3.7: Boxplot comparison CoM velocity and acceleration at the end of the first step in HC and PD. Asterisk indicates significant group difference ($p < 0.05$). Double asterisk indicates significant difference ($p < 0.01$)

In summary, while there were not any significant differences in the overall temporal sequence of GI and the dynamics of unloading between HC and PD, the properties

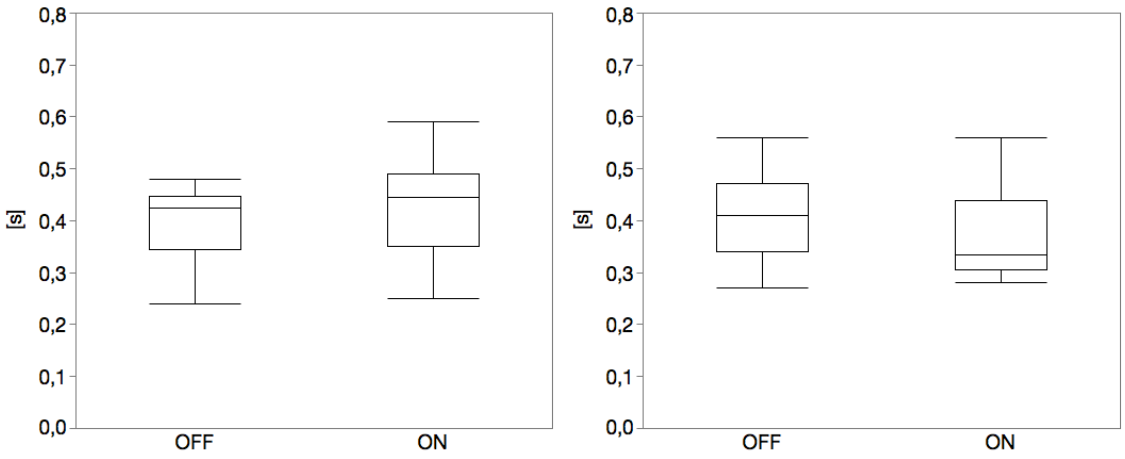
Parameter	**HC**	**PD-OFF**	**S**	**Z**	**p**
IM_DUR	0.385 (0.330-0.475)	0.395 (0.338-0.440)	663	-0.47	0.64
IM_COP_LEN	58.56 (47.65-78.67)	47.12 (25.32-57.25)	535	-2.81	**0.005***
IM_COP_VEL	159.11 (126.56-203.75)	125.51 (71.14-163.71)	566	-2.24	**0.025***
IM_COP_ML_DIS	42.38 (29.88-51.47)	32.64 (18.60-40.39)	568	-2.21	**0.0274***
IM_COP_AP_DIS	35.41 (24.49-48.47)	25.41 (14.30-40.49)	566	-2.24	**0.025***
IM_COP_ML_VEL	115.85 (85.59-135.33)	90.00 (44.55-114.93)	570	-2.17	**0.0301***
IM_COP_AP_VEL	91.18 (64.15-137.48)	72.75 (36.18-105.72)	588	-1.84	0.0659
IM_COM_ACC	0.73 (0.46-1.05)	0.54 (0.36-0.80)	586	-1.89	0.0593
IM_COM_COP_DIS	0.065 (0.048-0.083)	0.050 (0.030-0.063)	562	-2.34	**0.019***
IM_COM_COP_SLO	52.77 (44.01-59.60)	53.49 (40.51-58.25)	662	-0.49	0.62
UN_DUR	0.345 (0.310-0.423)	0.375 (0.318-0.468)	737	0.86	0.39
UN_COM_ACC	1.26 (1.03-1.57)	1.33 (1.12-1.79)	716	0.49	0.63
UN_COM_COP_DIS	0.075 (0.058-0.100)	0.090 (0.078-0.100)	751	1.13	0.26
FS_SL	0.565 (0.505-0.623)	0.460 (0.375-0.540)	494.5	-3.55	**0.0004***
FS_SL_%	63.21 (58.27-69.63)	49.89 (42.81-60.93)	490	-3.63	**0.0003***
FS_VEL_AVG	0.98 (0.88-1.13)	0.85 (0.70-1.05)	570	-2.17	**0.03***
FS_TOE_COM_VEL	0.83 (0.76-0.97)	0.69 (0.54-0.91)	517	-2.50	**0.0125***
FS_TOE_COM_ACC	1.86 (1.43-2.02)	1.37 (1.14-1.73)	530	-2.90	**0.0037***

Table 3.4: Comparison of temporospatial parameters of GI between HC and PD-OFF. All parameters are reported as median with the interquartile range in brackets. Asterisk indicates significant p-values.

of imbalance and the first step were altered in a highly significant manner, when compared to HC.

3.2.3 Effects of Levodopa on Gait Initiation in Patients with PD

To investigate the effect of dopamine substitution on GI parameters they were compared on a single-subject level via the Wilcoxon signed-rank test for twelve PD subjects, that completed the assessment in OFF and ON condition (Full results in table 3.5).



(a) Imbalance (b) Unloading

Figure 3.8: Boxplot comparison of GI phase durations in PD-OFF and PD-ON.

The temporal sequence did not change after levodopa intake in subjects with PD as the durations of Imbalance and unloading phase did not differ significantly (figure 3.8).

During imbalance three parameters were responsive to levodopa substitution and improved significantly. The CoP trajectory was longer after levodopa intake (figure 3.9) and CoP displacement was greater and faster in anteroposterior direction (figure 3.10). The percentage increase of CoP trajectory significantly correlated to the percentage increase in CoP amplitude in anteroposterior direction ($r = 0.66$, $p = 0.02$).

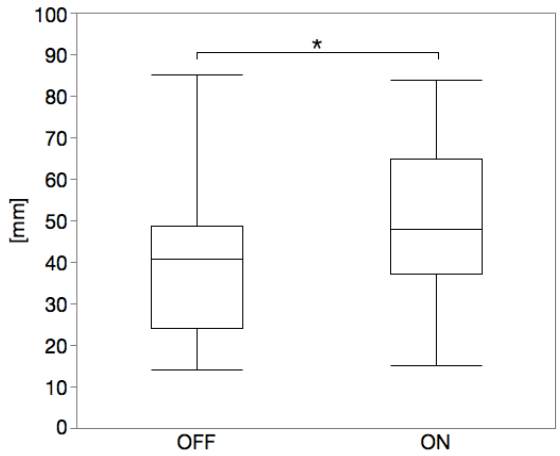
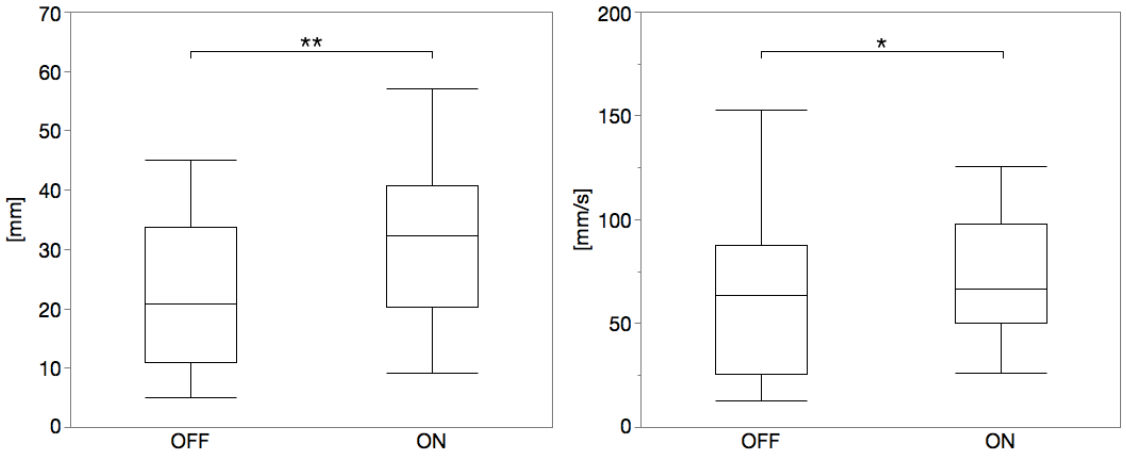


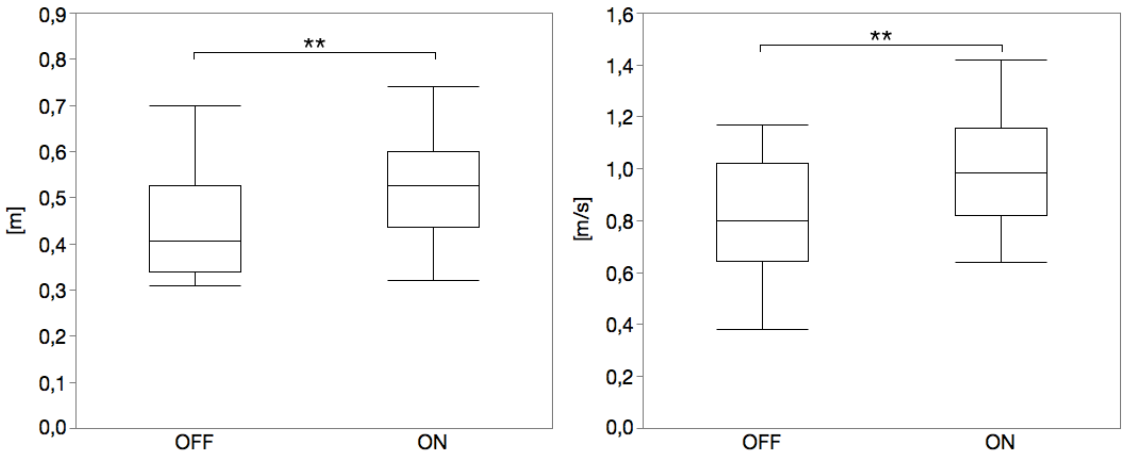
Figure 3.9: Boxplot comparison of length of CoP trajectory during imbalance between PD-OFF and PD-ON. Asterisk indicates significant group difference ($p < 0.05$).



(a) Anteroposterior CoP displacement (b) CoP velocity in anteroposterior direction

Figure 3.10: Boxplot comparison of CoP displacement and velocity in anteroposterior direction during imbalance between PD-OFF and PD-ON. Asterisk indicates significant group difference ($p < 0.05$). Double asterisk indicates significant difference ($p < 0.01$).

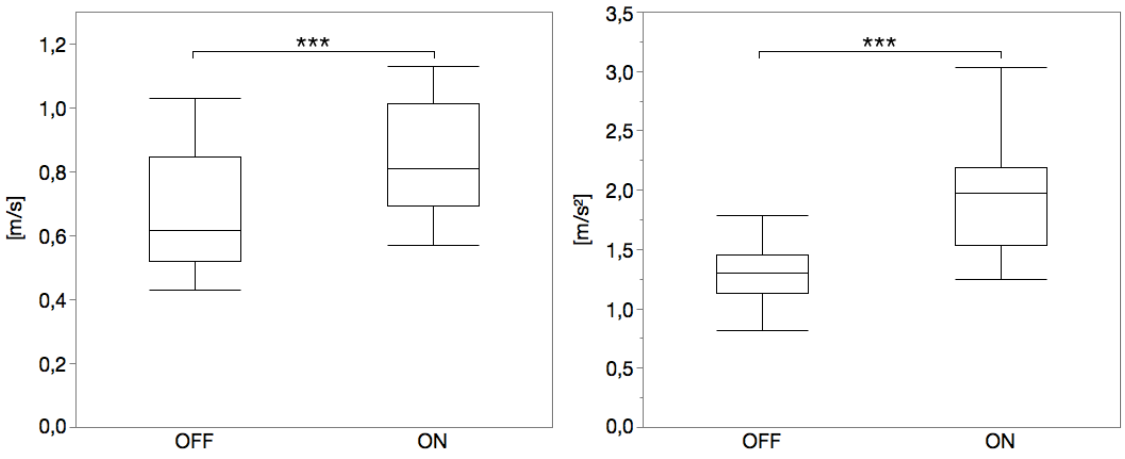
The properties of the first step were found to be highly responsive to dopamine substitution as it was longer and faster after the levodopa challenge (figure 3.11).



(a) Step length (b) Average velocity

Figure 3.11: Boxplot comparison of the first step between PD-OFF and PD-ON. Double asterisk indicates significant difference ($p < 0.01$).

Simultaneously the data demonstrated significantly increased CoM velocity and acceleration at the end of the first step, when subjects were in the ON condition.(figure 3.12).



(a) COM velocity (b) COM acceleration

Figure 3.12: Boxplot comparison of CoM velocity and acceleration at the end of the first step between PD-OFF and PD-ON. Triple asterisk indicates significant difference ($p < 0.001$).

All other parameters were not significantly affected by levodopa intake in this study's population. Still, noteworthy trends could be shown for the uncoupling of CoM and CoP at the end of imbalance ($p = 0.0659$; figure 3.13) and at the end of unloading

(p =0.0781; figure 3.14b). Similarly the CoM acceleration at the end of unloading trended to increased values in the ON condition (p = 0.064; figure 3.14a).

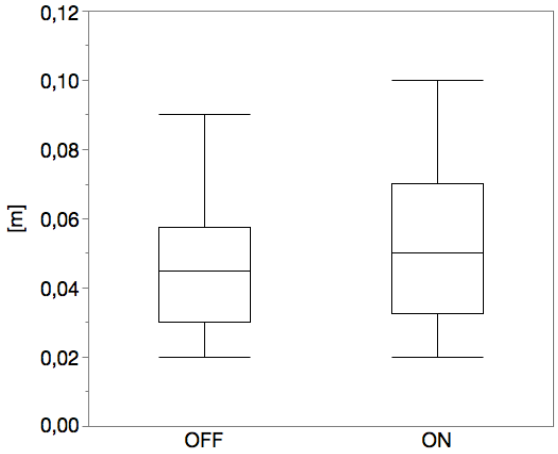
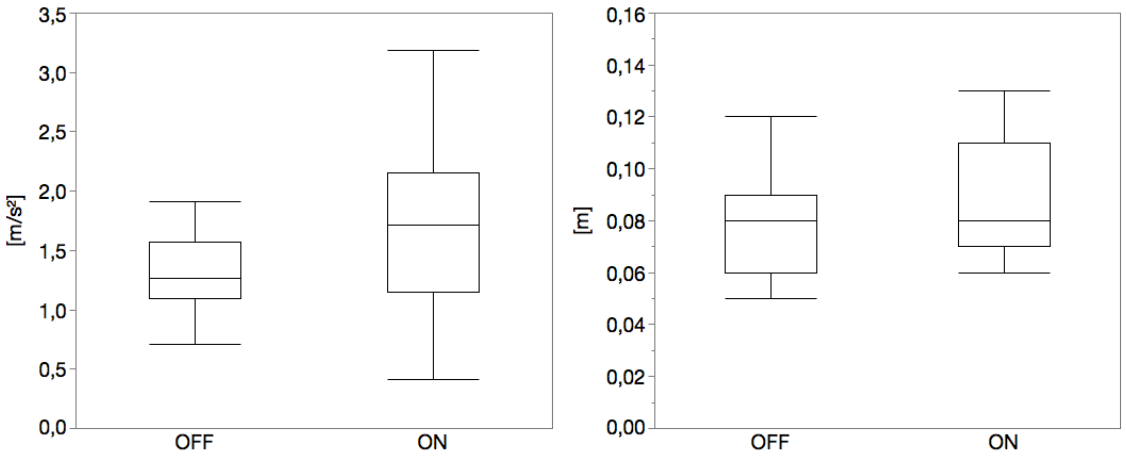


Figure 3.13: Boxplot comparison of the CoM/CoP displacement at the end of imbalance between PD-OFF and PD-ON.



(a) CoM acceleration

(b) CoM/CoP displacement

Figure 3.14: Boxplot comparison of CoM acceleration and displacement at the end of the unloading between PD-OFF and PD-ON.

To understand the interplay between the parameters, that improved after levodopa supplementation, a standard least square regression analysis was performed, that tried to predict the proportional changes of the respective parameters during the first step based on the alterations during imbalance in the individual subjects. Percentage alteration of imbalance could not be used to predict percentage improvement of the first step.

In conclusion the ON condition resulted in a longer and faster first step, while APA during imbalance was amplified and accelerated in anteroposterior direction as well. Regression analysis failed to provide a direct statistical link between the proportional alterations of GI parameters during the two phases. Furthermore, the ON condition was associated with noteable trends in the displacement of CoM and its acceleration throughout GI.

Parameter	**PD-OFF**	**PD-ON**	**S**	**p**
IM_DUR	0.425 (0.345-0.448)	0.445 (0.350-0.490)	14.5	0.2749
IM_COP_LEN	40.83 (24.15-48.67)	47.98 (37.29-65.00)	29.0	**0.021***
IM_COP_VEL	110.17 (57.35-133.90)	99.47 (75.36-169.64)	19.0	0.1514
IM_COP_ML_DIS	25.11 (17.96-37.41)	30.01 (25.67-51.87)	21.0	0.1099
IM_COP_AP_DIS	20.77 (10.91-33.77)	32.31 (20.36-40.68)	37.0	**0.0015***
IM_COP_ML_VEL	69.46 (42.74-102.06)	75.49 (49.98-135.82)	10.0	0.4697
IM_COP_AP_VEL	63.81 (25.74-87.47)	66.77 (50.32-97.94)	29.0	**0.021***
IM_COM_ACC	0.51 (0.39-0.86)	0.65 (0.53-0.97)	10.0	0.4697
IM_COM_COP_DIS	0.05 (0.03-0.06)	0.05 (0.03-0.07)	24.5	0.0859
IM_COM_COP_SLO	55.57 (51.04-61.62)	54.47 (42.90-61.49)	-17.0	0.2036
UN_DUR	0.410 (0.340-0.473)	0.335 (0.305-0.440)	-16.5	0.2354
UN_COM_ACC	1.27 (1.09-1.57)	1.72 (1.15-2.15)	24.0	0.064
UN_COM_COP_DIS	0.08 (0.06-0.09)	0.08 (0.07-0.11)	25.0	0.0781
FS_SL	0.405 (0.340-0.525)	0.525 (0.435-0.600)	37.5	**0.0015***
FS_SL_%	44.9 (39.3-56.1)	57.8 (49.4-67.5)	37.0	**0.0015***
FS_VEL_AVG	0.80 (0.64-1.02)	0.99 (0.82-1.16)	36.5	**0.002***
FS_TOE_COM_VEL	0.62 (0.52-0.85)	0.81 (0.69-1.02)	39.0	**0.0005***
FS_TOE_COM_ACC	1.31 (1.13-1.46)	1.97 (1.53-2.19)	39.0	**0.0005***

Table 3.5: Within-subject comparison of temporospatial parameters of GI between PD-OFF and PD-ON. All parameters are reported as median with the interquartile range in brackets. Asterisk indicates significant p-values.

3.3 Molecular Imaging

The descriptive data derived from molecular imaging is presented in table 3.6 for each region of interest. The provided values are the median and interquartile range refer to the respective hemisphere more or less affected by neurodegeneration. Normality of data could not be confirmed.

ROI	**More affected hemisphere**	**Less affected hemisphere**
CNC	1.31 (0.94-1.53)	1.41 (1.06-1.80)
PUT	1.13 (0.75-1.35)	1.18 (0.93-1.57)
STR	1.19 (0.88-1.41)	1.28 (0.99-1.64)
SMA	0.12 (0.05-0.21)	0.08 (-0.03-0.21)

Table 3.6: Median BP values for the investigated ROIs sorted by more resp. less affected hemisphere. IQR are reported in brackets.

3.4 Correlations of Biomechanics and Imaging

To explore the correlation between GI parameters and BPs a multivariate analysis was performed. As expected biomechanical parameters of GI and imaging data did correlate significantly within each respective category. The correlations between each biomechanical parameter of GI and the imaging data were characterized via Spearman's Rank Order Correlation Coefficient. The results showed significant correlations for the striatum in general as well as for the caudate nucleus and the putamen whenever they occurred (tables 6.1 to 6.18 in chapter 6). The data for the correlations between GI and tracer binding in striatum and the SMA is presented in table 3.7.

Parameter	Contralateral				Ipsilateral			
	STR		SMA		STR		SMA	
	Rho	p-value	Rho	p-value	Rho	p-value	Rho	p-value
IM_DUR	-0.38	0.09	0.06	0.77	-0.28	0.21	-0.09	0.70
IM_COP_LEN	0.58	**0.005***	0.45	**0.04***	0.61	**0.003***	0.27	0.22
IM_COP_VEL	0.54	**0.009***	0.38	0.08	0.57	**0.006***	0.21	0.34
IM_COP_ML_DIS	0.54	**0.01***	0.49	**0.02***	0.57	**0.006***	0.19	0.40
IM_COP_AP_DIS	0.50	**0.02***	0.61	**0.003***	0.55	**0.008***	0.48	**0.02***
IM_COP_ML_VEL	0.54	**0.01***	0.34	0.13	0.55	**0.008***	0.15	0.49
IM_COP_AP_VEL	0.50	**0.02***	0.50	**0.02***	0.52	**0.01***	0.42	0.05
IM_COM_ACC	0.57	**0.006***	0.46	**0.03***	0.51	**0.02***	0.38	0.07
IM_COM_COP_DIS	0.51	**0.01***	0.50	0.02	0.56	**0.007***	0.28	0.21
IM_COM_COP_SLO	-0.08	0.71	-0.28	0.21	0.05	0.83	-0.42	0.05
UN_DUR	-0.35	0.12	-0.36	0.10	-0.30	0.18	-0.17	0.47
UN_COM_ACC	0.30	0.18	0.35	0.11	0.33	0.13	0.35	0.11
UN_COM_COP_DIS	0.41	0.06	0.35	0.11	0.44	**0.04***	0.24	0.27
FS_SL	0.17	0.45	0.22	0.33	0.27	0.22	0.15	0.51
FS_SL%	0.30	0.17	0.16	0.47	0.37	0.09	0.16	0.47
FS_VEL_AVG	0.33	0.14	0.25	0.26	0.31	0.16	0.33	0.14
FS_TOE_COM_VEL	0.36	0.11	0.34	0.13	0.35	0.12	0.32	0.15
FS_TOE_COM_ACC	0.51	**0.01***	0.15	0.52	0.34	0.12	0.31	0.16

Table 3.7: Spearman's Rho ranked order correlations between BP and GI parameters. Asterisk indicates significant correlation ($p < 0.05$).

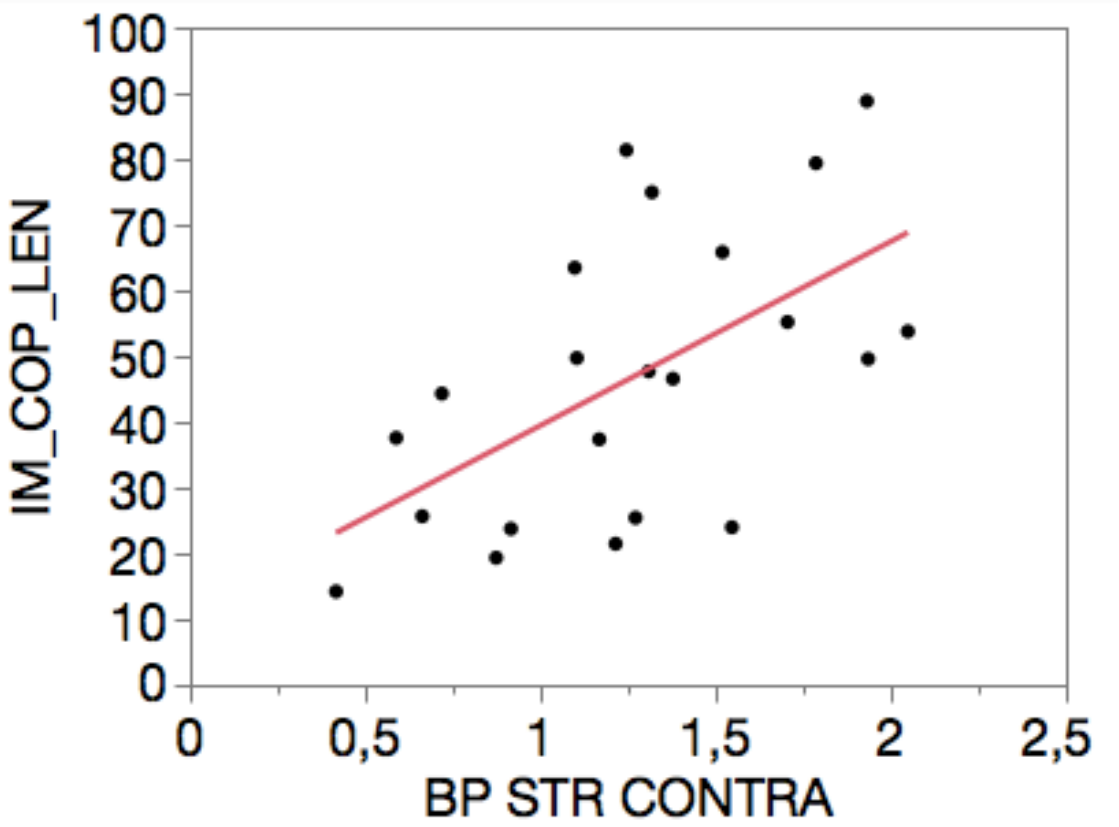
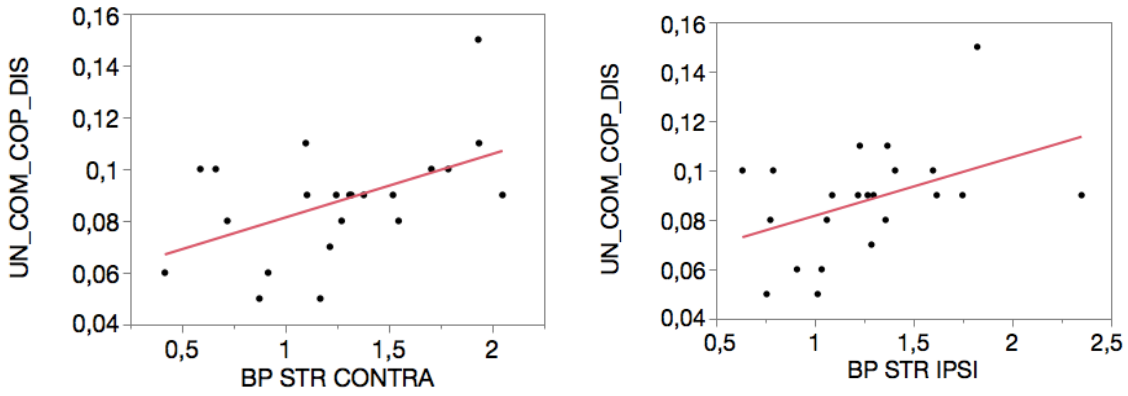


Figure 3.15: Linear correlation between the CoP trajectory during imbalance and the contralateral striatal tracer binding.

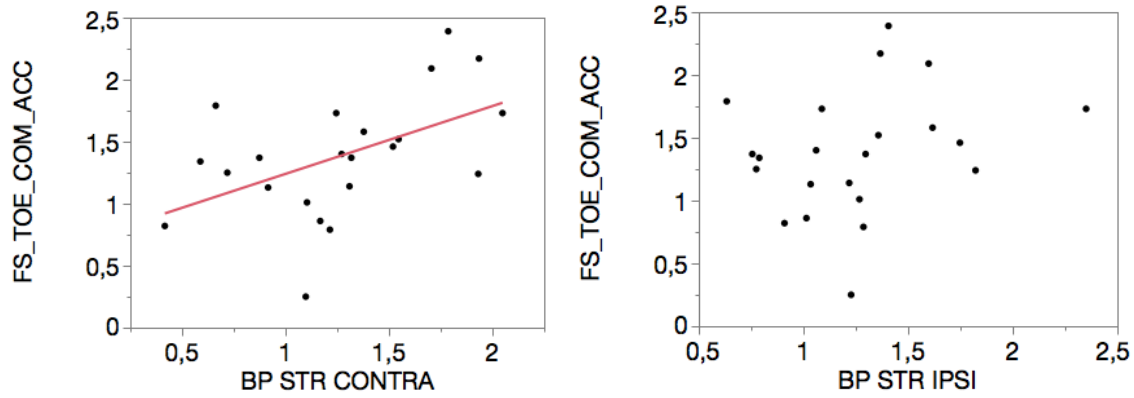
All GI parameters during imbalance and the CoM acceleration as well as the CoM/CoP uncoupling at end of imbalance were significantly correlated with bilateral striatal tracer binding. An exemplary correlation is presented in graph 3.15.

The CoM/CoP uncoupling at the end of unloading was significantly correlated with the ipsilateral striatal binding, while the correlation did hardly meet statistical significance for the contralateral side ($p = 0.06$; figure 3.16). The acceleration of CoM at the end of the first step did only correlate with contralateral tracer binding without any noticeable trend for ipsilateral binding ($p = 0.12$; figure 3.17).



(a) Contralateral (b) Ipsilateral

Figure 3.16: Linear correlations between CoM/CoP uncoupling at the end of unloading and the striatal tracer binding.



(a) Contralateral (b) Ipsilateral

Figure 3.17: Linear correlations between CoM acceleration at the end of the first step and the striatal tracer binding.

Five GI parameters were not only correlated to striatal tracer binding, but could also be linked to binding in the contralateral SMA. The length of the CoP trajectory during imbalance was significantly correlated to the binding potential in the contralateral SMA as were the respective displacement in mediolateral and anteroposterior direction. Similarly, the CoP velocity in anteroposterior direction during imbalance and the CoM acceleration at the end of imbalance were closley related to the contralateral SMA binding. The amplitude of APA in anteroposterior direction did not only show the strongest correlation to contralateral SMA binding potential ($p = 0.003$; figure 3.18), but did show significant correlation to the ipsilateral SMA, too ($p = 0.02$).

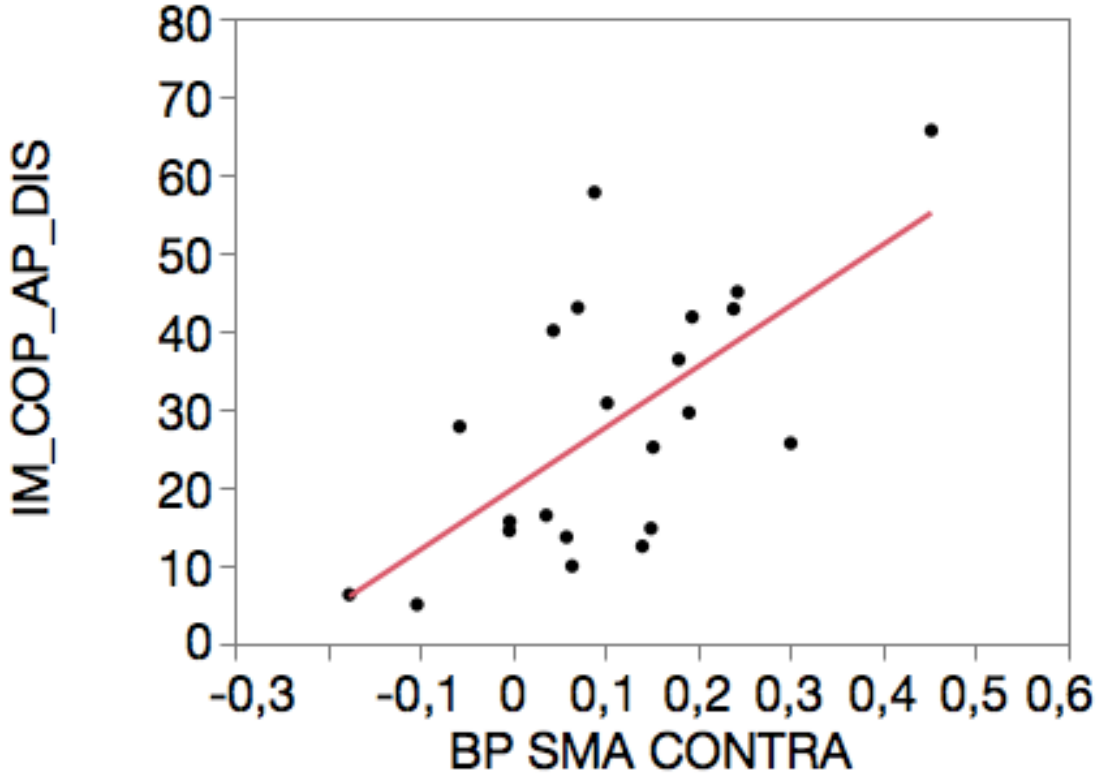


Figure 3.18: Linear correlation between the CoP displacement in anteroposterior direction during imbalance and the contralateral tracer binding in the SMA.

To further understand the statistical relationship between GI parameters and the imaging data, when they showed correlations on the striatal *and* the cortical (SMA) level, linear stepwise regression modeling was employed. Regression modeling took striatal and cortical BP in each hemisphere into consideration. The stepwise inclusion of factors was continued as long as the contribution of the next added factor to the model was statistically significant ($p < 0.05$). The identified factors, providing the best regression results, were furthermore assessed for independence via factorial modeling.

The contralateral striatal tracer binding was found to be the strongest and only statistically significant factor for modeling the length of the CoP trajectory ($p = 0.005$) and the CoP displacement in mediolateral direction ($p = 0.01$) during imbalance as well as the CoM acceleration at its end ($p = 0.02$).

CoP displacement and velocity in anteroposterior direction during imbalance were best predicted by models including BP of the contralateral SMA and the striatum. For both cases SMA functioned as the major contributor to the model ($p = 0.003$ and $p = 0.01$) compared to the striatal binding ($p = 0.03$ and $p = 0.04$). Even

though they correlate in between themselves the effects of the imaging values can be considered statistically independent from each other, as a factorial of both variables did not add any significance to a standard least squares regression model in both cases.

3.5 Summary

The results of this study could demonstrate significant alterations of GI performance specific to PD. Some, but not all of these alterations could be improved by levodopa substitution. Comparison of biomechanical and imaging data revealed significant correlations between dopaminergic innervation and APA.

It could be shown that several GI parameters are statistically dependent on the initial stance in healthy subjects, which were therefore considered to be too heavily confounded for further analysis. While the temporal sequence of GI and the assessed parameters during unloading remained preserved in PD, imbalance and the first step were significantly smaller and slower in all aspects. While the stepping performance was significantly improved in the ON condition, in postural adjustments only the anteroposterior CoP displacement during imbalance was responsive to drug condition in PD. Significant correlations could be made between cerebral dopaminergic activity and the extent and speed of APA during imbalance. While all these parameters did correlate with striatal activity, some did also correlate with cortical tracer binding. Further statistical analysis indicated a predominant correlation for APA amplitude and velocity in anteroposterior direction during imbalance and the cortical tracer binding, while the remaining parameters were primarily dependent on striatal tracer binding.

Chapter 4

Discussion

This study could further characterize the alterations in GI specific to PD and provided evidence indicating a significant contribution of the dopaminergic system to the execution of this motor task.

4.1 Experimental Design

As it was laid out in section 1.3.3 previous publications identified several factors, that significantly influence performance during gait initation in PD, which this study aimed to address by its experimental design. As multiple authors reported a benificial effect of cueing on GI in PD, the study design purposefully omitted the implementation of cues [11, 29, 30, 105].

Rocchi and others described a significant effect of initial standing conditions on the amplitude of APA during GI in both HC and PD [56, 115]. Biomechanical investigation of subjects with PD in quiet stance demonstrated impaired postural responses in PD, that were further emphasized in narrow stance width [57].

As altered stance is associated with PD, it has to be taken into account as a relevant contributor to GI performance in PD [2, 115]. Here it is argued, that standardization of initial stance, as has been practiced in several previous studies on GI, might obscure disease related alterations of stance and subsequently interfere with GI performance. Therefore, the experimental design refrained from enforcing fixed feet positions.

In a multivariate analysis of the data exploring the correlations of initial stance

width and GI twelve biomechanical parameters were significantly linked to the base of support in healthy subjects. While the choice of stance width might be influenced by other factors than disease, previous studies on GI in PD did not take this confounding factor, that physiologically modulates GI performance, into consideration. Normalization of the outcome variables with regards to the base of support would have been the desirable option, but currently the interplay between all factors determining stance width and its possibly complex effects on GI performance have yet to be determined and quantified. In a more conservative approach these parameters were excluded from further calculations to limit the scope of analysis to alterations specific to PD.

The findings of this part of the analysis were striking in that most (83 %) of "stance-dependent" parameters were affiliated with the unloading phase. This observation aligns with the finding of Honeine et al. in healthy subjects, linking increased stance width to increased amplitudes of mediolateral APA, when taking into consideration, that the main CoP shift in mediolateral direction during APA prior to stepping occurs during this phase. The current results refine the previous insights by suggesting, that stance width physiologically affects APAs particularly during unloading.

4.2 Specific Alterations of Gait Initiation in Patients with PD

By comparing GI performance in HC and PD-OFF several GI parameters could be identified, that were significantly altered specifically in PD.

The alterations in GI performance in PD in this data set were limited to two aspects of GI, imbalance and the first step. The early APA during imbalance was found to be significantly reduced in amplitude and velocity, reproducing results of previous investigations [18, 48, 105]. Two studies, that investigated GI in similar detail confirm the observation, that CoP displacements are less extensive and slower in PD specifically during imbalance [10, 37]. Early CoM acceleration and displacement at the end of imbalance were also impaired in PD, which is conclusive assuming these are directly determined by early postural changes.

Due to the significant effect of the initial stance most parameters characterizing unloading had to be excluded (see section 4.1). Previous findings, that indicate a specific effect of PD on GI performance in this phase and did not take stance width into consideration, can therefore neither be confirmed nor denied. The aspects of

unloading, which were not "stance-dependent", were found to be unaffected by PD in this data set.

The first step was significantly smaller and shorter in PD, which again is largely corroborated by the evidence in the literature [10, 105, 125]. Subsequently the parameters that indicate overall stepping efficacy, the CoM acceleration and the uncoupling of CoM and CoP at the end of the first step, were significantly smaller in PD.

The overall timing of GI phases, however, remained preserved in PD as data analysis failed to reveal any statistically significant effect of group affiliation on APA durations, which is in line with some of the previous published evidence [10, 11, 67, 85]. Other studies, which have reported increased APA durations in GI in PD, did in part employ cueing and thereby added a reaction task to the stepping task, which might explain contradictory evidence across the literature [30, 48, 18, 117].

Another possible explanation for variance in the results might arise from the different methodology, that was applied to identify discriminatory events on the time line. While studies reporting increased APA durations determined the onset of APA by establishing an arbitrary quantitative threshold, that detects a significant change in CoP displacement, this study determined APA onset by qualitative identification by the investigator [29, 114]. When movements decrease in fortitude, they tend to supersede a threshold at a later point in time, which might have influenced the temporal measurements based on a quantitative approach (figure 4.1). The qualitative approach used in this study limits the effect of this mechanism, that could introduce a significant bias into the calculations. The data at hand supports the hypothesis, that the physiological temporal sequence of GI is not significantly altered in PD patients.

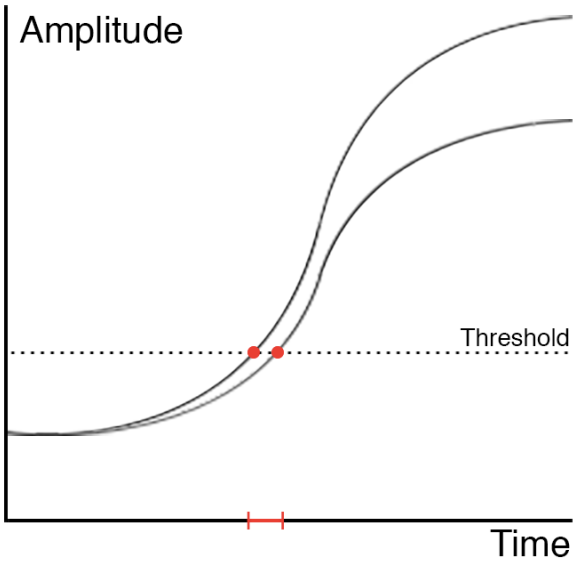


Figure 4.1: Schematic illustration of the influence of altered amplitude on threshold based event identification.

This study could reproduce findings of previous publications demonstrating bradykinetic alterations of GI performance in PD. In this data set these alterations manifested in changes of early APA and the first step. The data could not demonstrate a specific effect of PD on neither the timing of GI, nor the unloading phase. Whether the decreased stepping efficacy in PD patients is a direct result of impaired APA during imbalance or both are indicators of a common underlying pathophysiological mechanism can only be speculated at this point.

4.3 The Levodopa Effect on Gait Initiation in Patients with PD

The effect of levodopa substitution on GI was investigated by an intra individual matched pair analysis of GI parameters in PD in OFF and ON condition. Previous studies comparing GI on and off medication reported an overall improvement of APA amplitude, shortened phase durations and a more effective first step in the ON condition [18, 29, 114, 115].

In contrast to previous reports the temporal sequence of GI was not affected by medication. This finding corresponds with the previous observation of this study, that the temporal sequence did not show any significant alteration specific to PD in the data set at hand. Again, the diverging results might be explained by the reasons

pointed out in section 4.2.

With regards to the postural phase only the anteroposterior CoP displacement and its velocity, as well as the overall trajectory during imbalance were increased in PD-ON. The increased amplitude in anteroposterior direction likely causes the concurrent increase in overall CoP trajectory, as the former is in part dependent on the first and they prove to be correlated in a significant manner. All other parameters during the postural phase of GI remained unaffected by levodopa.

Hence, the levodopa-dependent improvement of mediolateral APA in GI described by previous authors could not be reproduced in this study. This may be due to our conservative approach that lead to the exclusion of the biomechanical parameters dependent on stance width, mostly involving the mediolateral displacement of the unloading phase.

In line with previous publications this data set demonstrated a significant improvement of the properties of the first step in ON. As the percentage alterations of the properties of the first step could not be predicted based on the percentage alterations of APA, it has to be assumed that stepping performance and anteroposterior APA improve independently after levodopa supplementation implicating distinct mechanisms at play.

4.4 Dopaminergic Loss and Gait Initiation

This is the first study to investigate the relationship between striatal dopaminergic denervation and gait initation in PD. While decreased presynaptic dopaminergic tone could be linked to overall disease severity in PD, only one previous study provided evidence linking it to specific aspects of motor perfomance [113, 122]. Isaias et al. demonstrated linear correlations between loss of dopaminergic innervation in the striatum (and its degree of asymmetry) and upper limb synergies.

The basal ganglia have been implicated in postural control by previous publications and are supposed to act as an "intermediary between the cerebral cortex and brainstem for automating the selection and execution of a context-specific postural response" [68, 128]. In the presented data linear correlations could be made between levels of striatal dopaminergic denervation and the amplitude and velocity of early APA during imbalance as well as early acceleration of CoM, further corroborating the relevance of the basal ganglia in postural control. The extent of displacement between CoM and CoP appeared to be linked to striatal dopaminergic tone through-

out GI as well, which is deemed indicative of efficient generation of APA. Decreasing amplitudes of this parameter have previously been associated with disease severity in PD [49].

The SMA has been shown to contribute to the timing of APA in healthy subjects and PD and it is demonstrably activated prior to their generation [67, 127]. In the current study the dopaminergic innervation on the cortical level in the SMA contralateral to the stepping leg stood in correlation with some aspects of the early postural adjustments during GI in PD linking the two. Subjects with pronounced cortical dopaminergic loss generated APAs, that were proportionally smaller and slower, than those with milder neuronal loss in the SMA. This observation emphasizes the relevance of the SMA as an important hub of the cortico-basal ganglia loop implicated in the feed forward aspect of postural control in GI [67].

The data points to a particularly close relationship between the anteroposterior aspect in APA and cortical dopaminergic innervation, which was the only GI parameter to be more reliably predicted by cortical than striatal dopaminergic activity and bilaterally expressed significant correlations with SMA. Additionally, this was the only aspect of APA, that was ameliorated by levodopa. Other works have shown postural control in anteroposterior dimension to be altered in a different manner than that in mediolateral dimension in PD during stance [58, 97]. This previous finding in combination with the current observations suggests the existence of two different neuronal correlates controlling postural responses in each respective dimension. Based on the current data it can be hypothesized, that anteroposterior postural control is dependent on cortical dopaminergic innervation in particular. This hypothesis derived from the current data beautifully corresponds with previous observations by Slobounov et al., who already found cortical activity specifically in the SMA to be related to anteroposterior balance control during standing [120].

It was remarkable, that while the stepping performance could be significantly improved by levodopa substitution in PD subjects, decreased stepping efficacy did not correlate directly with decreased levels of dopaminergic innervation. Thus it needs to be concluded, that the extent of dopaminergic loss does not directly determine deterioration of stepping performance. Still, the supplementation of levodopa improves the first step, which might be accomplished indirectly by improvement of the clinical condition in ON with reduced rigidity and overall bradykinesia.

4.5 Limitations of this Study

Several limitations of this study have to be taken into consideration, when interpreting its results. While it helped specifically identifying PD related alterations of GI, the exclusion of "stance-width dependent" outcome variables left a blind spot in the analysis. While it has been shown, that these parameters depend on stance width, it can not be excluded that they are significantly altered due to PD as well. To confirm or deny this assumption further work is necessary to establish a method to differentiate the two scenarios. The proposed method would need to be able to *control for the influence of initial stance without interfering with initial stance*, because the choice of stance width might be one of the variables afflicted by or compensating for the pathological impairment of GI in subjects with PD. This could be facilitated by approximating the size of the effect of initial stance on GI parameters and weighting the analysis or by determining the physiological individual stance width in PD subjects and enforcing it during data acquisition. Both approaches demand a more detailed insight into the factors affecting stance width and its effect on GI than is currently available.

With regards to the data derived from molecular imaging it has to be stated, that FP-CIT-SPECT has only been validated for the estimation of dopaminergic innervation in the striatal areas, which are comparably rich in DAT density. The SMA contains far fewer DAT and subsequently accumulates significantly less tracer molecules. As this difference in DAT expression negatively impacts the signal-to-noise ratio, the tracer should ideally be revalidated by a study linking imaging data to pathological examinations of the SMA. Nevertheless, the results of this study implicating the SMA in feed forward control are plausible, which in turn can be considered as weak evidence suggesting at least a certain degree of validity of the imaging data.

Even though the studied population can be considered to be sufficiently large and molecular imaging could be acquired for most PD patients, little more than a third did completed the levodopa challenge as well, because some patients were exhausted from the OFF trials. This reduced the sample size to as little as ten in some of the study's calculations. While this is not unreasonably little in comparison to previous publications, a more extensive data set might have provided even more reliable results. Another question, that could not be answered, is whether GI performance is linked to variance in striatal dopaminergic activity in healthy subjects as well, because imaging was only performed in subjects with PD.

Chapter 5

Conclusions

This study provides relevant insights into the specific alterations of GI, that occur in PD, and how these are affected by levodopa substitution. Beyond that, this study illuminated the interplay between residual cerebral dopaminergic activity and the performance of PD subjects during GI. A schematic overview of this study's findings is provided in figure 5.1

By controlling for anthropometrics and base of support this study could confirm, that early APA and the first step are significantly altered in PD independently of these variables. Previously published evidence, that indicates PD related alterations during the unloading of the stepping leg, needs to be reevaluated in light of the current observation. The significant effect of initial stance width on GI has most often been neglected in previous publications.

The observed effect of levodopa on GI and the correlation of dysfunction of GI with striatal dopaminergic loss in PD suggest a role of the depletion of the dopaminergic system in the impaired generation of early APA and the decline in stepping efficacy in PD. While dopamine likely influences stepping performance only indirectly, execution of early APAs is directly dependent on the levels of dopaminergic innervation.

Postural adjustments in anteroposterior direction were demonstrated to be uniquely sensitive to levodopa and to be primarily linked to the SMA, while mediolateral control was predominantly dependent on striatal dopaminergic innervation and was not levodopa sensitive. Of the alterations, that were directly dependent on dopaminergic loss, only those parameters, which were comparatively more affected by cortical

rather than striatal denervation, were levodopa sensitive. This observations can be employed to phrase the hypothesis, that postural control during GI is conveyed via different neuronal mechanisms for the anteroposterior and mediolateral direction.

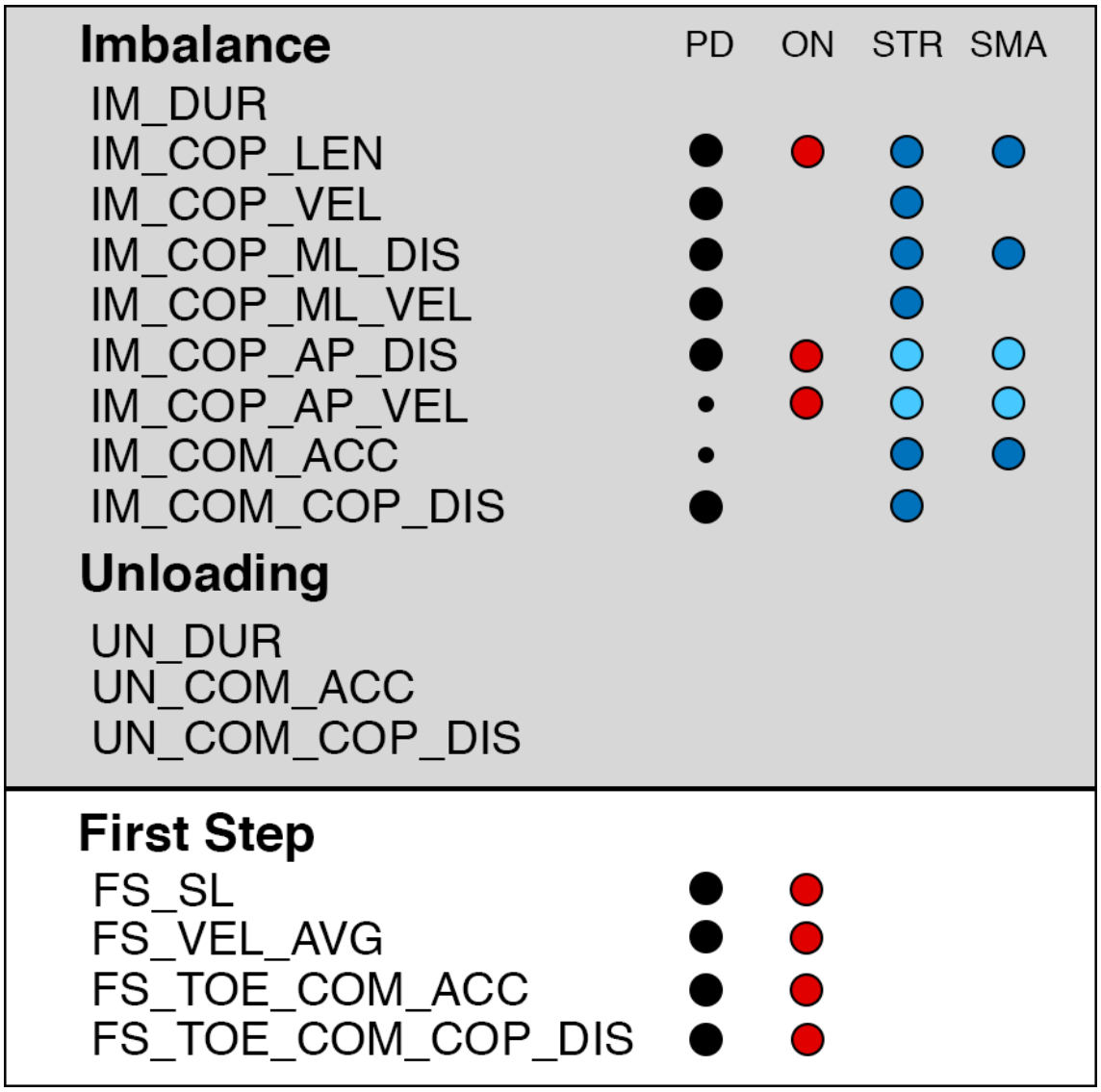


Figure 5.1: Illustrated summary of this study's results. Large circles indicate statistically significant effect of Parkinson's Disease (PD), medication state (ON), bilateral striatal (STR) or cortical (SMA) dopaminergic innervation on the respective parameter. Small circles indicate a noteworthy trend in the data suggesting a possible effect of PD. Dark blue circles represent predominant correlation of GI performance with striatal tracer binding, while light blue circles indicate predominant correlation with cortical tracer binding.

In conclusion, this study did not only provide insights into the specific impairments during GI in PD and its relationship to the dysfunctional dopaminergic system, but also allowed for more fundamental extrapolations about postural control during

GI, that has been shown to be physiologically modulated by stance width primarily during unloading of the stepping leg. The association of imaging data with GI performance suggests the existence of two distinct mechanisms for anteroposterior and mediolateral aspects of postural control and implicates a specific contribution of dopaminergic neurons in the SMA to anticipatory postural control in anteroposterior direction.

5.1 Perspective

While the presented results confirmed the hypothesis of this study, that dysfunction of the dopaminergic system plays an important role in impaired execution of GI in PD, several questions remain unanswered.

This study's findings suggest a crucial role of initial stance on those dynamics of anticipatory postural control, which facilitate unloading of the stepping leg during GI. This raises the need to further specify the biomechanical interplay between stance width and GI to understand its alterations in PD. Weighted modeling based on a biomechanical data set of sufficient size could provide additional insight to this regard. As stance width modulates APA generation physiotherapeutic interventions focusing on stance width prior to stepping could be devised and potentially be utilized to improve GI performance in PD patients.

Ultimately, the question whether the timing of APA is altered in PD remains unresolved. It can be attempted to further explore the temporal aspects of GI by quantitatively comparing the differences in outcome measures, that are brought about by the different approaches, that have been employed to determine the onset of APA. Ideally a standardized methodology should be established, that is independent from investigatorial input *and* amplitude of the subsequent APA, to work towards putting this issue at rest.

Further research is needed to develop a precise understanding of the mechanism by which levodopa substitution improves stepping performance in PD. As striatal and cortical dopaminergic denervation did not determine the degree of impairment, it might be affected via dopamine-dependent indirect modulation of neuronal networks outside of the dopaminergic system. Future investigations using additional molecular tracers could possibly link GI performance to other neurotransmitter systems. Decreased thalamic cholinergic activity, for instance, has been linked to an increased postural instability in PD [9, 99]. This implicates a role of this specific transmitter

system in postural control, that might pertain GI as well.

Finally, the current investigation establishes the feasibility of the utilized methodology. It can now be employed to investigate the role of dopaminergic denervation with regards to distinct alterations in GI in PD patients suffering from specific gait impairments such as FoG. Conceivably this line of research holds the potential to extend the current comprehension of the pathophysiological mechanism behind these gait impairments.

Chapter 6

Appendix

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Parameter	Side	ROI	Rho	p-value
IM_DUR	C	CNC	-0.37	0.09
	C	PUT	-0.36	0.09
	C	STR	-0.37	0.09
	C	SMA	0.07	0.77
	I	CNC	-0.31	0.16
	I	PUT	-0.26	0.25
	I	STR	-0.28	0.21
	I	SMA	-0.09	0.70

Table 6.1: Spearman's Rank Order Correlations for the duration of the imbalance phase (IM_DUR) and imaging values.

Parameter	Side	ROI	Rho	p-value
IM_COP_LEN	C	CNC	0.57	**0.006***
	C	PUT	0.59	**0.004***
	C	STR	0.58	**0.005***
	C	SMA	0.45	**0.037***
	I	CNC	0.54	**0.01***
	I	PUT	0.60	**0.003***
	I	STR	0.61	**0.003***
	I	SMA	0.27	0.22

Table 6.2: Spearman's Rank Order Correlations for the length of the CoP trajectory during imbalance phase (IM_COP_LEN) and imaging values.

Parameter	Side	ROI	Rho	p-value
IM_COP_ML_DIS	C	CNC	0.50	**0.017***
	C	PUT	0.54	**0.009***
	C	STR	0.54	**0.01***
	C	SMA	0.49	**0.02***
	I	CNC	0.46	**0.033***
	I	PUT	0.58	**0.005***
	I	STR	0.61	**0.003***
	I	SMA	0.19	0.404

Table 6.3: Spearman's Rank Order Correlations for the displacement of the CoP trajectory during imbalance phase (IM_COP_ML_DIS) and imaging values.

Parameter	Side	ROI	Rho	p-value
IM_COP_AP_DIS	C	CNC	0.49	**0.021***
	C	PUT	0.52	**0.014***
	C	STR	0.50	**0.019***
	C	SMA	0.61	**0.003***
	I	CNC	0.51	**0.016***
	I	PUT	0.54	**0.01***
	I	STR	0.55	**0.008***
	I	SMA	0.48	**0.023***

Table 6.4: Spearman's Rank Order Correlations for the displacement of the CoP trajectory during imbalance phase (IM_COP_AP_DIS) and imaging values.

Parameter	Side	ROI	Rho	p-value
IM_COP_ML_VEL	C	CNC	0.52	**0.014***
	C	PUT	0.54	**0.01***
	C	STR	0.54	**0.01***
	C	SMA	0.34	0.13
	I	CNC	0.48	**0.023***
	I	PUT	0.53	**0.011***
	I	STR	0.55	**0.008***
	I	SMA	0.16	0.49

Table 6.5: Spearman's Rank Order Correlations for the average velocity of medio-lateral CoP displacement during imbalance phase (IM_COP_ML_VEL) and imaging values.

Parameter	Side	ROI	Rho	p-value
IM_COP_AP_VEL	C	CNC	0.49	**0.019***
	C	PUT	0.51	**0.014***
	C	STR	0.50	**0.017***
	C	SMA	0.50	**0.017***
	I	CNC	0.52	**0.012***
	I	PUT	0.50	**0.017***
	I	STR	0.53	**0.011***
	I	SMA	0.42	0.051

Table 6.6: Spearman's Rank Order Correlations for the average velocity of antero-lateral CoP displacement during imbalance phase (IM_COP_AP_VEL) and imaging values.

Parameter	Side	ROI	Rho	p-value
IM_COP_VEL_AVG	C	CNC	0.53	**0.012***
	C	PUT	0.54	**0.009***
	C	STR	0.54	**0.009***
	C	SMA	0.38	0.084
	I	CNC	0.52	**0.013***
	I	PUT	0.53	**0.01***
	I	STR	0.57	**0.006***
	I	SMA	0.21	0.342

Table 6.7: Spearman's Rank Order Correlations for the average velocity of CoP displacement during imbalance phase (IM_COP_VEL_AVG) and imaging values.

Parameter	Side	ROI	Rho	p-value
IM_COM_ACC	C	CNC	0.52	**0.014***
	C	PUT	0.57	**0.006***
	C	STR	0.57	**0.006***
	C	SMA	0.46	**0.033***
	I	CNC	0.35	0.108
	I	PUT	0.55	**0.008***
	I	STR	0.51	**0.016***
	I	SMA	0.39	0.074

Table 6.8: Spearman's Rank Order Correlations for the acceleration of CoM at the end of the imbalance phase (IM_COM_ACC) and imaging values.

Parameter	Side	ROI	Rho	p-value
IM_COM_COP_DIS	C	CNC	0.50	**0.018***
	C	PUT	0.52	**0.012***
	C	STR	0.51	**0.015***
	C	SMA	0.50	**0.017***
	I	CNC	0.45	**0.036***
	I	PUT	0.56	**0.006***
	I	STR	0.56	**0.007***
	I	SMA	0.28	0.210

Table 6.9: Spearman's Rank Order Correlations for the distance between CoM and CoP at the end of the imbalance phase (IM_COM_COP_DIS) and imaging values.

Parameter	Side	ROI	Rho	p-value
IM_COM_COP_SLO	C	CNC	-0.09	0.676
	C	PUT	-0.11	0.640
	C	STR	-0.08	0.710
	C	SMA	-0.28	0.210
	I	CNC	0.03	0.887
	I	PUT	-0.00	0.986
	I	STR	0.05	0.832
	I	SMA	-0.42	0.053

Table 6.10: Spearman's Rank Order Correlations for the slope of the vector between CoM and CoP at the end of the imbalance phase (IM_COM_COP_SLO) and imaging values.

Parameter	Side	ROI	Rho	p-value
UN_DUR	C	CNC	-0.30	0.167
	C	PUT	-0.39	0.074
	C	STR	-0.34	0.115
	C	SMA	-0.36	0.104
	I	CNC	-0.26	0.241
	I	PUT	-0.27	0.233
	I	STR	-0.30	0.181
	I	SMA	-0.17	0.459

Table 6.11: Spearman's Rank Order Correlations for the duration of the unloading phase (UN_DUR) and imaging values.

Parameter	Side	ROI	Rho	p-value
UN_COM_ACC	C	CNC	0.33	0.132
	C	PUT	0.28	0.202
	C	STR	0.30	0.177
	C	SMA	0.35	0.112
	I	CNC	0.23	0.311
	I	PUT	0.40	0.068
	I	STR	0.33	0.132
	I	SMA	0.35	0.113

Table 6.12: Spearman's Rank Order Correlations for the acceleration of CoM displacement at the end of unloading phase (UN_COM_ACC) and imaging values.

Parameter	Side	ROI	Rho	p-value
UN_COM_COP_DIS	C	CNC	0.43	**0.045***
	C	PUT	0.39	0.071
	C	STR	0.41	0.059
	C	SMA	0.35	0.109
	I	CNC	0.34	0.117
	I	PUT	0.46	**0.033***
	I	STR	0.44	**0.042***
	I	SMA	0.24	0.273

Table 6.13: Spearman's Rank Order Correlations for the distance between CoM and CoP at the end of unloading phase (UN_COM_COP_DIS) and imaging values.

Parameter	Side	ROI	Rho	p-value
FS_SL	C	CNC	0.24	0.284
	C	PUT	0.17	0.446
	C	STR	0.17	0.452
	C	SMA	0.22	0.326
	I	CNC	0.30	0.18
	I	PUT	0.24	0.278
	I	STR	0.27	0.223
	I	SMA	0.15	0.512

Table 6.14: Spearman's Rank Order Correlations for the length of the first step (FS_SL) and imaging values.

Parameter	Side	ROI	Rho	p-value
FS_SL_%	C	CNC	0.35	0.113
	C	PUT	0.32	0.146
	C	STR	0.30	0.172
	C	SMA	0.16	0.468
	I	CNC	0.38	0.079
	I	PUT	0.34	0.126
	I	STR	0.37	0.092
	I	SMA	0.16	0.474

Table 6.15: Spearman's Rank Order Correlations for the normalised length of the first step (FS_SL_%) and imaging values.

Parameter	Side	ROI	Rho	p-value
FS_VEL_AVG	C	CNC	0.33	0.137
	C	PUT	0.36	0.099
	C	STR	0.33	0.139
	C	SMA	0.25	0.261
	I	CNC	0.30	0.181
	I	PUT	0.32	0.145
	I	STR	0.31	0.158
	I	SMA	0.33	0.14

Table 6.16: Spearman's Rank Order Correlations for the average velocity during the first step (FS_VEL_AVG) and imaging values.

Parameter	Side	ROI	Rho	p-value
FS_TOE_COM_VEL	C	CNC	0.39	0.082
	C	PUT	0.36	0.11
	C	STR	0.36	0.112
	C	SMA	0.34	0.133
	I	CNC	0.36	0.104
	I	PUT	0.33	0.14
	I	STR	0.35	0.124
	I	SMA	0.32	0.153

Table 6.17: Spearman's Rank Order Correlations for the velocity of CoM at the toe off of the stance leg (FS_TOE_COM_VEL) and imaging values.

Parameter	**Side**	**ROI**	**Rho**	**p-value**
FS_TOE_COM_ACC	C	CNC	0.51	**0.016***
	C	PUT	0.54	**0.009***
	C	STR	0.55	**0.008***
	C	SMA	0.15	0.518
	I	CNC	0.20	0.368
	I	PUT	0.40	0.068
	I	STR	0.34	0.12
	I	SMA	0.31	0.16

Table 6.18: Spearman's Rank Order Correlations for the acceleration of CoM at the toe off of the stance leg (FS_TOE_COM_ACC) and imaging values.

Subject ID	Disease Duration (years)	Age at Onset	Hoehn & Yahr	UPDRS III (OFF)	UPDRS III (ON)
PD01	12	60	2,5	37	17
PD02	19	40	2,5	28	12
PD03	5	40	2	33	12
PD04	10	45	2,5	31	5
PD05	11	40	2	17	5
PD06	11	42	2	25	5
PD07	5	66	3	N/A	N/A
PD08	9	63	2	N/A	N/A
PD09	17	45	3	47	22
PD10	13	55	2,5	27	12
PD11	8	60	2	12	4
PD12	12	55	2	31	19
PD13	20	43	2	35	9
PD14	9	47	2	23	7
PD15	12	40	2	41	8
PD16	12	50	2	34	19
PD17	20	36	3	37	10
PD18	11	46	3	46	8
PD19	12	42	2	49	4
PD20	9	61	3	22	17
PD21	7	65	2	20	14
PD22	18	46	3	26	17
PD23	19	46	3	34	10
PD24	7	54	2	28	13
PD25	5	65	2	30	22
PD26	4	51	2	14	5
PD27	2	49	2	13	5

Table 6.19: Clinical properties of PD patients

List of Abbreviations

APA	Anticipatory Postural Adjustments
DBS	Deep Brain Stimulation
GPI	Globus Pallidum Internus
FP-CIT	[^{123}I]-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane
COMT	Catechol-O-Methyltransferase
CoM	Centre of Mass
CoP	Centre of Pressure
FoG	Freezing of Gait
GI	Gait Initiation
HC	Healthy Controls
LAM	Laboratorio per l'Analisi del Movimento
LRRK2	Leucine-rich Repeat Kinase 2
MDS	Motor Disorder Society
MAO-B	Monoamine Oxidase B
PET	Positron Emission Tomography
PD	Parkinson's Disease
PPN	Pedunculo Pontine Nuclei
SMA	Supplementary Motor Area
SPECT	Single-photon Emission Computed Tomography
STN	Nucleus subthalamicus
UKW	Universitätsklinikum Würzburg
UPDRS	Unified Parkinson's Disease Rating Scale

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